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TASK FORCE ON PRESCRIPTION DRUGS

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DRUG PRESCRIBERS

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TASK FORCE ON PRESCRIPTION DRUGS

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TABLE OF CONTENTS

Chapter Page

TERMINOLOGY VII
INTRODUCTION IX

PART A—RATIONAL PRESCRIBING

1. THERAPEUTIC JUDGMENTS 3
   Drug Efficacy and Safety 3
   Drug Evaluation 4
   Combination Drugs 4
   Drug Interaction 5
   Multiple Prescribing 5

2. THE TEACHING OF PHARMACOLOGY 6
   Course Content 6
   Clinical Applications 7

3. PRESCRIBER INFORMATION 9
   Medical Journals 10
   Journals of Prescribing 11
   Government Journals 12
   Drug Compendia 12
   Formularies 12
   Textbooks 13
   Industry Advertising 13
   Detail Men 14
   Drug Samples 15
   Postgraduate Education 15

   REFERENCES 16

PART B—DRUG QUALITY

4. INTRODUCTION 21

5. CLINICAL EQUIVALENCY 22
   Clinical and Biological Equivalency 23
   Factors in Biological Equivalency 23
   Formulation Factors 24

Chapter *Page*

6. DRUG STANDARDS 25
   Compendia Standards 25
   Adequacy of Compendia Standards 26
   Public Versus Private Compendia 30

7. QUALITY CONTROL 31
   Federal Drug Legislation 31
   FDA Activities 32
   Division of Biologics Standards 37

8. TASK FORCE EQUIVALENCY TRIALS 39

REFERENCES 40

PART C—FORMULARIES

9. INTRODUCTION 43
   History 43

10. AMERICAN FORMULARIES 44
   U.S. Pharmacopeia 44
   The National Formulary 44
   Homeopathic Pharmacopoeia of the United States 45
   AMA Publications 45
   Accepted Dental Remedies 45

11. STATE FORMULARIES 46
   Formulary Structure 46
   Advantages and Disadvantages 47

12. OTHER FORMULARIES 48
   Private Insurance Programs 48
   Hospital Formularies 48
   Foreign 48
   Drug Lists 49

REFERENCES 50

LIST OF TABLES

Table I **Page**

Food and Drug Administration Regulatory Program Data (Drugs), Fiscal Year 1967 34

LIST OF FIGURES

Figure I **Page**

Hypothetical Blood Level Curves for "High Peak" (A) and "Low Peak" (B) Products 28

TERMINOLOGY

The term *generic equivalents* is not used in the body of this report. Although it has been widely utilized, it has been given so many different interpretations that it has become confusing. Instead, the following terms are used:

Chemical equivalents.—Those multiple-source drug products which contain essentially identical amounts of the identical active ingredients, in identical dosage forms, and which meet existing physiochemical standards in the official compendia.

Biological equivalents.—Those chemical equivalents which, when administered in the same amounts, will provide essentially the same biological or physiological availability, as measured by blood levels, etc.

Clinical equivalents.—Those chemical equivalents which, when administered in the same amounts, will provide essentially the same therapeutic effect as measured by the control of a symptom or a disease.

The following terms are also used:

Generic name.—The *established* or *official* name given to a drug or drug product.

Brand name.—The registered trademark name given to a specific drug product by its manufacturer.

INTRODUCTION

In May of 1967, acting upon a directive from the President, John W. Gardner—then Secretary of Health, Education, and Welfare—established the Task Force on Prescription Drugs. The charge to the Task Force appeared to be simple—

Undertake a comprehensive study of the problems of including the cost of prescription drugs under Medicare.

Few assignments, however, have been more complex. Essential for the Task Force study was objective information on the health needs and resources of the elderly; the present patterns of drug use; the nature of drug research, production, and distribution; current drug insurance programs in the United States and abroad; reimbursement methods and administrative approaches; legal and fiscal aspects; and the pharmacological and clinical aspects, including the intricate problem of chemical and clinical equivalency of generic products.

In some instances, the necessary data were readily available. In others, they were not—and the Task Force found it necessary to undertake its own special research projects.

The information derived from these studies serves as the basis for the findings and recommendations which are being published separately by the Task Force. In addition, however, this basic material appears to have great value for the Congress, many State and Federal governmental agencies, the medical and pharmacy communities, the drug industry, health insurance organizations, health educators, and consumer groups. Accordingly, the Task Force is publishing the detailed results of its studies in a series of background papers.

Incorporated in this volume are three closely related subjects—an analysis of some of the prescribing patterns of physicians and the types of training and sources of information available to them; a consideration of drug quality, together with the currently controversial matter of chemical, biological, and clinical equivalency; and a brief discussion of the major types of drug formularies currently available to prescribers.

The material was prepared by the Task Force staff in cooperation with many consultants, both governmental and nongovernmental, whose invaluable assistance is gratefully acknowledged. Particular appreciation goes to the scores of distinguished clinicians, pharmacologists and medical educators who graciously provided their assistance in preparation of the section on rational prescribing—to the university, industry, governmental and other scientists who offered advice and counsel in developing the section on drug quality, and in initiating the Task Force clinical drug trials—and to the representatives of the *U.S. Pharmacopeia*, the *National Formulary*, and other leading compendia who assisted in preparation of the section on formularies.

It is our hope that this publication will not only serve as the basis for careful analysis and discussion, but will help to improve the quality of health care for all Americans.

Philip R. Lee

PHILIP R. LEE, M.D.

PART A

RATIONAL PRESCRIBING

Chapter 1

THERAPEUTIC JUDGMENTS

The act of writing a drug prescription is one of the most ancient and most visible symbols of the physician's knowledge and experience. In each case, it is the sum of judgments concerning the efficacy and safety of the drug for the problem at hand, alternative forms of therapy, expected clinical results, possible side effects, the most appropriate dosage form, the length and intensity of treatment, and the possible deleterious effects of drug interaction. Sound judgments on these matters should result in the right drug for the right patient in the right amounts at the right time—in short, rational prescribing.

Selection of the right drug is, however, only part of the story. The physician first faces the problem of establishing a diagnosis—which can be much more difficult than selecting the appropriate medication. The technical resources needed by the physician to make an optimal drug selection under rapidly changing clinical conditions may be unavailable, costly, time-consuming, or simply inefficient. The conscientious physician, then, must attempt to match the ideal of rational prescribing against the reality of diagnostic information which is not always complete or perfect.

There is still another aspect of drug therapy that many feel should be mentioned in any discussion of rational prescribing—the matter of cost. According to this view, prescribing an expensive drug which is merely the modification of another equally useful product available at lower cost, or prescribing an expensive combination of drugs which offers no particular therapeutic advantage, would not be rational therapy.

It has been held that rational prescribing, as described above, is far from universal in medical practice. A clinical pharmacologist at Harvard has written:

> "It is my belief that lack of knowledge and sophistication in the proper therapeutic use of drugs is perhaps the greatest deficiency of the average American physician today." (*24*)

Others are at least in agreement that prescribing practices could be improved. Among factors which have contributed to the problem are cited the following:

- Inadequate training in the clinical applications of drug knowledge during the undergraduate medical curriculum; (*24*)
- Inadequate sources of objective information about drug properties and indications available to practicing physicians; (*5*)
- Widespread reliance by prescribers for continuing education upon advertising and promotional materials distributed by drug manufacturers; (*6*)
- Exceedingly rapid turnover in the popularity of prescription drug specialties; (*28*) and
- The limited time available to practicing physicians to examine, evaluate, and maintain currency with the therapeutic claims for newly marketed products. (*29*)

Because rational prescribing is so essential not only to patient care but also to the success of a drug insurance program, it is important to examine the factors which influence drug selection, and the medical school training and postgraduate sources of information that may serve as a basis for these selections.

Drug Efficacy and Safety

It is elemental that physicians would prescribe only those drugs of proven efficacy and safety and, since the Kefauver-Harris Amendments of 1962, no new drugs have legally been permitted to enter interstate commerce without such proof.[1]

A drug which meets these requirements would presumably be safe and efficacious, with its claims kept in conformity. Yet the literature includes reports of unexpected side effects and lack of claimed efficacy discovered well after products have entered the market. Of this, a pharmacologist has written:

> "The probable incidence of reactions caused by drug allergy, intolerance, idiosyncrasy, and

---

[1] Under its new organization and more rigid requirements, FDA rejected five times as many New Drug Applications in fiscal year 1967 than it approved. Of those rejected, 45 percent lacked sufficient animal test data; 72 percent were deficient in proof of safety in human trials; 76 percent were lacking in clinical efficacy; and others were rejected on technical grounds.

drug interaction cannot be determined in preclinical investigation in animals or even in man. These are rare events that are identified and measured after a large and broad general clinical experience in man. Under our present system it usually takes 2 or 3 years of clinical experience before the full potential for harm as well as the limits of utility is realized. It has been suggested that a probationary period of about that length of time be considered by the medical profession for all new drugs." (*30*)

Drug Evaluation

The complexity of drug evaluation has also been considered by an author of one of the standard textbooks of pharmacology. "The drug-efficacy complex," he stated, "can be viewed as composed of the amazingly intricate interaction of three major components, the drug, the patient, and the physician." Among these components and sub-components—nearly all of which must be considered by the individual physician in selecting any drug—he included the following: (*19*)

DRUG FACTORS

- **Doses employed**
- **Multiple effects**
- **Absorption**
- **Distribution**
- **Metabolic fate**
- **Excretion**
- **Duration of effect**
- **Route, duration of administration**
- **Habituation**
- **Addiction liability**
- **Tolerance**
- **Side effects**
- **Toxicity**
- **Idiosyncrasy, hypersensitivity**
- **Margin of safety**
- **Precautions**
- **Contraindications**
- **Pharmaceutical properties**
- **Chemical properties**
- **Drug interactions**

PATIENT FACTORS

- **Sex, age**
- **Body size and weight**
- **Pregnancy**
- **Pharmacogenetic factors**
- **Biochemical status**
- **Nutritional status**
- **Drug metabolism**
- **Disease (vast multiplicity of factors)**
- **Idiosyncrasy, hypersensitivity**
- **Contraindications, precautions**
- **Toxicity**
- **Margin of safety**
- **Concomitant therapy**
- **Personality factors**
- **Attitude toward disease, drugs, doctors**
- **Cost**

PHYSICIAN FACTORS

- **Training**
- **Diagnostic skill**
- **Therapeutic skill**
- **Experience with drugs**
- **Concomitant therapy**
- **Attitude toward drug therapy**
- **Attitude toward patient**
- **Attitude toward disease**

Critical evaluation of utility versus possible side effects is particularly important in the use of highly potent drugs, for it is among this group that toxicity—anticipated as well as unanticipated—is also likely to be greater.

Of this, he said:

> ". . . claims for efficacy must always be assessed within the framework of safety under discrete conditions of recommended clinical use. The good physician does this very thing *every* time he prescribes a drug. He weighs the expected benefits to be derived against the potential dangers involved. On occasion, in a person with a life-threatening illness, he may administer a highly toxic agent with a narrow margin of safety, if there is a reasonable chance of helping his patient." (*19*)

Combination Drugs

For many years, manufacturers have employed the concept of multiple drug therapy in the development of fixed drug combinations, and during the past 20 years, the use of such combinations—many of them patented or trademarked—has become increasingly popular. Today their number actually exceeds by half the number of products containing a single active drug, and their use extends to virtually all therapeutic categories. The rate at which new combinations are introduced, however, has been declining in recent years.

In some instances, the use of more than a single drug at the same time can produce a more salutory effect, often in lower dosage, than when full doses of the agents are used separately. Diphenylhydantoin is often prescribed in combination with phenobarbital, for example, in the treatment of convulsive disorders, and combinations of the early sulfonamides have been used to minimize the risk of kidney damage attendant upon the use of a single agent.

But the widespread reliance upon combinations has generated sharp criticism. The Council on Drugs of the American Medical Association has long held the prescribing of drug mixtures to be irrational. (*44*) One authority on antimicrobial therapy has written:

> "Actually, except in tuberculosis and a rare form of infection of heart valves, combined use of drugs [in infectious diseases] is of little value, except in desperate situations before the physician has adequate information about what bacterial infection is occurring and must use his clinical judgment.
>
> "A careful review of fixed branded combinations on the market, including combinations of penicillin and sulfonamides, penicillin and streptomycin, tetracycline and antifungal agents, and tetracycline and novobiocin, does not substantiate the claims that the combination is superior to one of the agents used separately. These combinations are expensive, deny the physician flexibility in dosage, are primarily promotional devices, and have the inherent problem that the patient undergoes the risk of serious adverse reaction to two or more drugs rather than to a single defined agent. The physician cannot determine which component is causing trouble if a bad reaction is encountered. I personally believe that we would do much better without these preparations." (*26*)

Among other arguments cited against the widespread use of fixed combination drugs are these:

- The combination is often given a trade name distinct from the names of the component drugs, and often bearing no relation to them, and thus does not readily identify the components to the physician.
- Although savings are achieved in some cases, in others the fixed combination is significantly more expensive than the total cost of the ingredients dispensed separately.

Those who favor the use of fixed combinations point out that they can help to reduce the risk of patient error, especially among the elderly, when more than one drug is being used. They also cite the convenience of such combinations to patients under long-term treatment, especially where the dose ratio of ingredients is not likely to change.

Drug Interaction

Although the simultaneous use of two or more drugs may permit a reduction in the necessary dose of each component, produce an enhanced clinical effect, and reduce toxicity, the opposite effects also may occur because of the interaction of the components. This has been the subject of intensive study both in and out of the Federal Government. In some cases, it has been discovered, drugs given over a period of time can stimulate not only their own metabolism but also that of other drugs given simultaneously—a phenomenon called "enzyme induction." In studying the investigative data submitted in support of new drugs, the Food and Drug Administration gives particular attention to these phenomena, particularly if drugs are to be marketed in fixed combination. (*18*)

Multiple Prescribing

Concern has also been expressed, especially among clinical pharmacologists, about the extensive use of drugs in today's society. In his summation of a recent conference on the scientific, social, and commercial aspects of prescribing, Paul Talalay wrote:

> "Some of the participants felt that the average doctor tends to over-prescribe; he orders unnecessary medicines, the wrong medicines, and too many medicines for the same illness, and he is too easily persuaded to change to the latest product." (*39*)

Charges of this kind, however, are hardly new. As far back as 1887, a professor of pharmacology in Germany complained that ". . . a great number of physicians, without rhyme or reason, go after every new remedy that is recommended to them. If an industrialist is but shrewd enough to advertise sufficiently, he usually succeeds in increasing the sale of his product—for some time at least—and thus enriching himself." (*40*)

The hazards of multiple prescribing have been well documented. In a study of patients hospitalized during 1962 to 1966, for example, it was found that an overall average of 10 percent experienced ill effects from the administration of drugs. The study indicated that the adverse reaction rate rose sharply with increasing use of drugs. Among those receiving between 6 and 10 drugs, the rate was 7 percent, while those receiving 16 to 20 drugs had a reaction rate of 40 percent. (*7*)

Chapter 2

THE TEACHING OF PHARMACOLOGY

American physicians are introduced to the principles of drug therapy early in their medical school training, but it has been claimed that, because of the rapid pace of drug introduction and obsolescence, much of this hard-won knowledge is outdated even before medical school graduation.

With few exceptions, medical training in the United States and Canada takes four years, of which the first two are preclinical—concentrating upon the scientific principles that underlie the practice of medicine. The third and fourth years offer less formal classroom and laboratory study, and bring the student into closer contact with patients and with practicing physicians who serve on the medical faculty. It is generally during the second preclinical year that the main course in pharmacology is offered, and, in most cases, it is the student's only formal exposure to the subject.

Pharmacology has been perhaps the subject of more debate and less recent change than any other medical discipline, and those who teach the subject appear to be among its severest critics. Part of the problem, these educators maintain, is that pharmacology is taught as a basic science when, in reality, it is a clinical science as well. As a result, the clinical uses of drugs receive scant and insufficient attention.

Of this, the President of the American Medical Association said recently:

> "There appears to be a growing feeling that pharmacology as a discipline is in some trouble, within the academic, medical community. It appears to me . . . that there has never been a time when pharmacologists and excellent pharmacologic education were needed more. . . .
>
> "Certainly there needs to be a recognition by all elements concerned with medical education that pharmacological principles should not and cannot be limited to a single or conservative series of courses given fairly early in the curriculum of the modern medical student, which almost universally now includes 4 years of medical school and 4 more years of internship and residency.
>
> "The goal of pharmacologic teaching is not a theoretical one. It is not limited to action at the molecular level. It must in part be practical and it should include information concerning the safe and effective use of drugs. A key principle is that all drugs are potentially toxic. The student as well as the practicing physician must remain continually aware of the possibility that any drug may do harm as well as good. Such continual awareness comes only from repeated exposure to pharmacologic education." (*44*)

And he stated:

> "It is my belief, which I share with many other people who are concerned with this problem, that ideally students should be educated in pharmacology in such a way that as physicians they will have the basic tools for continued learning about new drugs and new developments in therapeutics that will appear during their years of active practice. Furthermore, they should be educated so that during the years of practice they will be oriented to the continuing education of pharmacologic experts in medical schools and not to the advertising of pharmaceutical manufacturers." (*44*)

Another problem is the apparent shortage of well-trained clinical pharmacologists to provide the more clinically-oriented courses. In most schools, pharmacology is taught mainly—and, in some cases, exclusively—by basic scientists whose interest in clinical drug developments cannot be expected to parallel that of the clinical pharmacologist. Although the number of clinical pharmacologists holding medical degrees is increasing, there is little immediate prospect of the demand being met. (*41*)

Course Content

The basic course in pharmacology follows roughly the same outline in most schools. It includes:

- Principles of drug action, such as absorption, distribution, metabolism, mechanism of action, tissue storage, toxicity, and excretion.
- Review of specific drug groups.

- Laboratory demonstrations.
- Prescription writing.

In addition to these basic features, some schools have introduced new concepts in attempts to make the course more relevant to the needs of the student during his clinical years in medical school and beyond.

Design of Drug Trials.—In at least one British medical school, students in the preclinical years are given instruction on the principles of controlled drug evaluation in the belief that "all practicing doctors should know something about its principles." (*4*)

Evaluation of Drug Advertising.—From 1957 until 1961, the students at Albany Medical College were exposed to a project in the evaluation of drug claims, as part of the basic pharmacology course. The project, comprising four sessions totalling 11 hours of class time, consisted of evaluating the references given in randomly-selected drug advertisements; amplifying the data through correspondence with the manufacturer and by reference to the published literature; and discussing the advertisements and collected data with invited company representatives. The originator of the project reported in 1960 that the students rated 11 of 26 companies reliable in their advertising claims. (*15*) He has recently suggested that the same project, conducted in the present setting of increased FDA surveillance of drug advertising, and using the same criteria, would reveal more than 70 percent to be reliable. (*16*)

Similar programs at the Universities of Alberta and British Columbia revealed that "the nature of the teaching of pharmacology with respect to claims for new drugs has a profound effect on the relevant attitudes of medical students." It was found that the attitudes of the teachers themselves appeared to reinforce the skepticism of students, and that this skepticism appeared to persist up to the time of medical school graduation. (*9*)

Clinical Applications

Aware of the need to bridge the gap between pharmacology as a basic and as a clinical science, several schools have begun to offer advanced courses during the clinical years of medical school.

Harvard University.—In addition to taking the basic course, which is taught in conjunction with pathophysiology, the students at Harvard are exposed at the beginning of the clinical curriculum to the socioeconomic aspects of drug promotion and use. An advanced pharmacology elective is offered in the fourth year, using a seminar approach and actual case histories. Particular attention is given to the problem of drug interaction and adverse drug reactions. Although the elective is limited to 35 students, about twice that many apply each year.

The pharmacologist in charge of the advanced course commented to the Task Force:

> "A course in pharmacotherapeutics and clinical pharmacology should be a required part of the curriculum in all American medical schools . . . Such a course would correlate the facts imparted to the student in the preclinical pharmacology course with his more recently acquired knowledge of the pathophysiology and the clinical aspects of disease states.
>
> "While such a course would have a great deal of important current information to impart to the soon-to-be-physician, I would see its major role in the development of proper scientific and critical attitudes towards pharmacotherapy. The development of such attitudes is absolutely essential to prepare the physician for a lifetime of scientific pharmacotherapy and of rational attitudes towards newly appearing drugs. Such a clinically oriented course in pharmacotherapeutics can be taught neither by basic pharmacologists nor by the majority of clinicians. It should be coordinated and largely taught by clinical pharmacologists, although pharmacotherapeutically-oriented clinicians would be expected to make valuable contributions." (*24*)

Columbia University.—In addition to the basic pharmacology course, Columbia requires of all students a second course, devoted to medical therapeutics and applied pharmacology. Initially limited to fourth-year students, the course has been extended to involve third-year students as well. Fifteen 1- to 2-hour sessions are given each year. Where possible, the basic science aspects of pharmacology are integrated with clinical applications. (*22*)

University of Florida.—Pharmacology is spread over a 3-year period beginning in the second year. The introductory course emphasizes the chemical basis of pharmacology; the lectures may also follow an organ system approach but cover only a few systems. During the third year, pharmacology is included in the internal medicine clerkships, and involves 15 hours of lecture-discussion on clinical problems. There is some teaching of drug therapy during patient visits on ward rounds. The final course is given in the fourth year, is required for all students, and occupies one month full-time. The approach is largely physiological and pathophysiological, and deals with organ systems, such as heart and brain. It also reinforces the basic science learned in the second year, and integrates it with the student's overall clinical experience. The course is taught by clinical pharmacologists, basic pharmacologists, and selected clinicians. (*27*)

Stanford University.—The pharmacology program comprises two courses which may be taken, at the student's option, at any time during his first three years at Stanford. Generally, second-year students will take these courses. The first deals exclusively with general principles, and encompasses not only the usual material on absorption, distribution, excretion, and metabolism of drugs, but also fundamental concepts of drug toxicity, carcinogenesis, mutagenesis, tolerance, addiction, the development of new drugs, clinical trials, and the evaluation of drugs. This course is considered a prerequisite for further study in pharmacology and therapeutics.

The second course offered by the pharmacology department is more like a traditional pharmacology course and covers systematic pharmacology. The major drug groups, cardiovascular agents, hormones, drugs affecting the central nervous system, etc., are discussed from both a basic and an applied point of view. This course is considered an introduction to the clinical use of drugs.

In addition to these basic courses, the department hopes to develop, in conjunction with appropriate clinical departments, shorter elective courses in restricted areas, such as the anticancer drugs, cardiovascular and renal drugs, and the like. These courses would extend deeply into clinical applications, and would be designed for the more advanced medical student. (*2*)

Temple University.—During the 1967–68 academic year, Temple offered for the first time a senior elective in clinical pharmacology. The full-time 7-week course included 4 hours a week of formal lectures and attendance at outpatient clinics observing patients who are undergoing drug therapy, and discussing the results of treatment with staff physicians and clinical pharmacologists. (*33*)

University of Chicago.—Supplementing the basic second-year course in pharmacology and toxicology at Chicago are discussions of a socioeconomic and scientific character, including drug costs, the nature of the drug industry, physician-pharmacist relationships, and the correlation of basic pharmacology and clinical drug use. In addition, a senior-year elective (chosen by about half the class) includes about 20 lectures and discussions of drug therapy, using the case history approach. A clinical pharmacologist teaches this elective and also serves on the attending staff. (*36*)

Chapter 3

PRESCRIBER INFORMATION

The practicing physician has at his command a therapeutic arsenal which includes some 1,200 generally available drugs and an additional 6,000 drug combinations, most of them marketed in a number of different dosage forms. The rate of drug introduction and obsolescence is such that the market life of a newly introduced drug product averages only about 5 years, and 70 percent of currently marketed drugs were either unknown or unavailable 15 years ago, when more than half of the Nation's physicians were receiving their pharmacology training in medical school.

In this setting, the physician's need for objective, well-organized and concise drug information is obvious. The sources of drug information, if not all objective, are at least legion. Among them are the following:

- Medical journals. Some 1,500 journals are published regularly in the United States. Most carry articles of a general nature, including many about new drugs and new studies of older ones, along with substantial portions of the issues consisting of drug advertising. A very few journals are devoted exclusively to drug therapy.
- Drug compendia. Volumes of drug information are readily available, including one widely-used reference book that is distributed with industry support to all practicing physicians without charge.[1]
- Formularies. Usually published by the pharmacy and therapeutics committees of hospitals, these are felt by many to be an educational as well as a cost-controlling device.[1]
- Textbooks of pharmacology and manuals of drug therapy.
- Professional society meetings and conventions.
- Postgraduate seminars, hospital staff meetings and, in some areas, radio and closed-circuit television conferences.
- The visits of drug company representatives or detail men.
- Mailings of drug advertisements and drug samples.
- Information supplied by hospital and community pharmacists.

Despite the heavy and continuing flow of information to prescribers, responsible medical educators and clinicians maintain that the average physician does not have sufficient access to unbiased source material nor time to sift out the objective data needed to facilitate rational therapeutic decisions. One professor of pharmacology recently stated:

> "It might be said that the physician has available to him the scientific literature and can make his judgment about the relative value of drugs from the literature.
>
> "This is just not so—the physician does not have the time.
>
> "I am a pharmacologist and my professional role is to keep up with drugs and I am unable to do so. I subclassify myself as a neuropharmacologist, which means I only have to keep up with drugs which act on the brain. In terms of original literature, I wonder if I even accomplish keeping up with this narrowed field.
>
> "Time is not the only problem, for a high percentage of the clinical and drug studies reported in the literature are paid by the parent drug house and this should be clear, the major pharmaceutical manufacturers do not support comparative studies which might show their product to be inferior. In a sense, they would be foolish if they did so, and their stockholders should correct them, since their object is to sell their drugs."

Then he added:

> "Most drug studies which are in the literature, even the good ones, controlled studies, are paid for by manufacturers, and manufacturers are not interested in comparing their drug with a similar drug, unless they have evidence that their drug is clearly superior to the similar drug." (45)

Others have expressed similar views. An authority on preventive medicine recently testified:

---

[1] These are discussed in more detail in the section beginning on p. 43.

> ". . . One has to be blind, deaf, and dumb, to lock his office, if he wishes to avoid being deluged with direct mail advertising, visits by detail men, and more recently heavy promotion in throwaway unsolicited journals which, for the most part, serve as advertising vehicles. One can read in the financial sections of the newspapers about the success of these throwaway journals, which, in my opinion, are taking a tremendous toll in trying to take over medical education. Booths are set up in hospitals and agents of drug firms walk the floors.
>
> "I have no objection to ethical promotion of products, but the matter is out of hand." (*26*, p. 714)

The drug industry appears firm in its belief that drugs are promoted fairly and responsibly. In a recent speech to his company's stockholders, the president of a large drug firm asked:

> "Who is better qualified than the pharmaceutical company to describe the qualities and performance of its drugs? It knows their history from genesis to application. It has the biggest stake in making certain that complete and accurate information is provided, because it is vital to the company that the physician obtain good, not bad, results with its products. If the company fails to do the communicating job right, it risks not only its investment in research, development, production, and marketing—it risks its reputation for integrity. Is it not therefore in the public interest that a company be identified with and be responsible for the products its makes and sells?" (*14*)

This belief would appear to be confirmed by studies which show that information supplied by drug manufacturers is an important determinant of drug use by physicians. (*8*)

Because the volume and nature of drug information available to prescribers has been the subject of continuing controversy, it appears worthwhile to consider its various sources and effects upon the selection and use of drugs.

Medical Journals

Because journals vary significantly in content and approach, some authors have, for descriptive purposes, placed them in the following categories: (*3, 21*)

Group I.—Controlled-circulation publications which are sent free to all prescribers or to selected prescriber populations. These are supported almost entirely by drug advertising. The editorial content varies among:

- summaries of current medical literature (e.g., *Modern Medicine*, *Current Medical Digest*);
- original articles (e.g., *Hospital Medicine*);
- feature stories on recent medical developments (e.g., *Medical World News*, *Medical Tribune*);
- advice on practice management and personal economic matters (e.g., *Medical Economics*, *Physician's Management*);
- articles of a philosophical or cultural nature, more or less related to the life sciences (e.g., *Medical Opinion and Review*, *MD Medical Newsmagazine*); and
- articles on leisure activities (e.g., *Rx: Golf and Travel*).

Many of these journals reach nearly all of the estimated 200,000 practicing physicians. Others are intended for distribution among selected medical specialty groups. At least one such journal is targeted at those physicians known to be the most prolific drug prescribers. Of this market—which has been dubbed the "H.P.P.'s," or "High Prescribing Practitioners"—Reis and Morando have written:

> "The philosophy behind the high-prescribing practitioner list is a simple one. It provides the manufacturer with the opportunity to make steady users of any given drug out of the most prolific users of drugs generally. To accomplish this, the 'H.P.P.' list uses the concept of marketing selectivity: directing promotion to physicians who are proven high-volume prescribers.
>
> "While no one has been able to determine whether these physicians are more intelligent, better organized, or just more energetic, than their colleagues, it can be seen why they may nevertheless be thought of, in certain quarters, as 'Superdoctors.'" (*35*)

Group II.—Journals of general medical interest paid for by individual subscription (e.g., *New England Journal of Medicine*, *Postgraduate Medicine*). Many of these journals also obtain significant support from drug advertising. Some of them, notably the *New England Journal of Medicine*, have, for a considerable time, maintained strict codes for the acceptability of drug advertising. The code of the *New England Journal*, adopted in 1958, has been superseded by several recent requirements of FDA advertising regulations. In summary, the code requires the following:

1. The generic or official name of a product must be stated.

2. Combinations of products in which the effectiveness of any of the individual components is found to suffer because of their combination are unacceptable.

3. The quantity of active substance or substances in each unit must be, and the recommended dosage should be stated.

4. The clinical evaluation of every new product must have been published or have been accepted for publication in the medical literature.

5. Adequate warning regarding toxic effects must be given, and narcotic or habit-forming drugs must be so designated.

6. Claims made for a product must be reasonable and well substantiated. *(10)*

Group III.—Journals of specialty interest. The various specialties—e.g., surgery, pediatrics, and obstetrics—are each represented by from one to six or more journals.

Group IV.—National, State and regional association journals. These journals, generally published by medical societies, tend to concentrate more on organizational than clinical matters. One author has said of them:

> "The trend is to de-emphasize the clinical and to concentrate on medical organizations, public relations, methods of influencing public opinion, the creation of good will for physicians and their organization, adequacy of medical facility, fees, cost of hospital care, legislation affecting the medical profession, public health, medical education, social security, relative values, third parties, and similar subjects . . ." *(43)*

Group V.—County and city health agency bulletins.

Group VI.—Journals of the allied medical professions (nursing, pharmacy, etc.)

Group VII.—Company-published journals. Like those in Group I, these are controlled-circulation publications which are sent to selected physician population groups. For the most part, they contain material of practical clinical application. Advertisements are included with these journals but promotional material is seldom, if ever, made part of the editorial content. A number of the company journals have gained wide acceptance and respect by the medical community, reflecting the serious effort and considerable funds expended in their production. For example, CIBA's *Clinical Symposia*—famed for its medical illustrations—cost the company some $1,200,000 between 1960 and 1967. *(23)*

Journals of Prescribing

Although several journals of pharmacology and experimental therapeutics are published in the United States, these are mainly technical in content and are generally of little practical aid to the prescriber. Three publications, however, exemplify recent attempts to provide objective drug information in easily assimilable form. These are *The Medical Letter*, *Pharmacology for Physicians*, and *Clin-Alert*.

Now in its 10th year, *The Medical Letter* is published by Drug and Therapeutic Information, Inc., without advertising. Its unsigned articles are a distillation of scientific reports and consultants' evaluation of the efficacy, safety, rationality, and occasionally the costs of specific drugs and drug combinations. Its conclusions are brief and to the point, and can be sharply critical. It is available only by subscription, but is purchased for distribution to their physician staffs by some group practice organizations, and for use by students in some medical and pharmacy schools. Its current circulation is about 38,000.

The Medical Letter was considered in a recent survey of physician impressions of various drug information sources conducted by the Opinion Research Corporation for the Pharmaceutical Manufacturers Association. Among a sample of 505 practicing physicians (the sample excluded those primarily engaged in hospital-based patient care), *The Medical Letter* was rated as follows: *(31)*

	Percent
"The One I Use Most Often"	2
"Use Frequently"	15
"Use Occasionally"	24
"Heard Of, but Never Use"	37
"Never Heard Of"	19
"No Answer"	3

Significantly, the publication finds greater favor among medical students and hospital-based physicians, such as interns, residents, and faculty. *(20)*

Another newsletter type of drug information journal, now in its third year, is *Pharmacology for Physicians*, which is published by the American Society for Pharmacology and Experimental Therapeutics. Each monthly issue contains a single review article on a specific group of drugs, written by a guest author. Individual products are not evaluated as such nor are economic factors considered. Most of the reviews are written by teaching pharmacologists, but some are prepared by industry scientists. No drug advertising is included in this publication.

A third publication, *Clin-Alert*, is published by Science Editors, Inc., of Louisville, Ky. It consists largely of abstracts from the printed literature on adverse reactions to drug therapy. References to the original articles are included, as well as previously cited references dealing with the same drug. *Clin-Alert* includes no drug advertising.

Government Journals

Since 1961, the British Government has supported the publication and distribution of *Prescribers Journal* to British physicians. It is self-described as ". . . an independent journal compiled by a representative Committee of Management supported by an Advisory Panel." (*11*) Published in pocket-size format, the journal appears bimonthly and consists of brief reviews of individual drugs or groups of drugs. The drugs are described by generic name, but are also identified by brand name where appropriate. As with *The Medical Letter*, it undertakes to evaluate newly-marketed drugs as well as older ones. The author of each article is identified.

Prescribers Journal also attempts to measure effectiveness against cost, and has been highly critical of noncontributory, duplicative products and combinations.

Government-supported journals are also distributed in Australia and New Zealand. In Sweden, a similar journal is scheduled to begin publication early in 1969.

Drug Compendia

A number of publications provide prescribers with information on drugs in common use. Some, such as Modell's *Drugs of Choice*, provide comparative data as well. Others, notably *New Drugs*, published by the American Medical Association, provide useful data on recent introductions. By far the most popular, and—according to a recent survey—described as the most useful is *Physicians' Desk Reference* (*PDR*).

Now in its 22nd edition, *PDR* is distributed without charge to all practicing physicians. As noted elsewhere,[2] it derives its support from a relatively limited number of drug manufacturers—primarily brand-name manufacturers—who pay for the space used in describing their products. The 2,600 products listed in the current edition are cross-indexed alphabetically by brand name, by manufacturer, by therapeutic indication, and by generic name and pharmacological action. Also included is a product identification section which pictures 800 products in full color to facilitate the identification of commonly used dosage forms. Since the product descriptions in *PDR* are regarded as "labeling," they must conform with the full-disclosure requirements stipulated in FDA regulations.

Among physicians included in the Opinion Research Corporation sample for PMA, *PDR* was evaluated as a source of prescribing information as follows: (*31*)

	Percent
"The One I Use Most Often"	82
"Use Frequently"	12
"Use Occasionally"	5
"Heard Of, but Never Use"	1
"Never Heard Of"	0
"No Answer", less than	½

Formularies[3]

Where they exist, drug formularies—even when they are not restrictive—are thought by their proponents to have a useful role in the promotion of rational prescribing. Used mainly by hospital staffs, the formulary has been defined as:

> ". . . a dynamic, ever-changing selective compilation of up-to-date information on modern pharmaceuticals. It is a book or booklet listing drugs and dosage forms, together with information about them, such as their use, method of distribution within the individual hospital, and other subject matter related to therapy, which the Pharmacy and Therapeutics Committee of each hospital staff wishes to include for the information of its staff.

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[2] See p. 50.

[3] See also p. 43.

> "The formulary system is a method used by the medical staff of a hospital, working through a Pharmacy and Therapeutics Committee, to evaluate and to select, from among the numerous medicinal agents available, those that are considered most useful therapeutically and to list dosage forms in which they may be administered most effectively. (*1*)

The Director of Montefiore Hospital described in recent Senate testimony the operation of the formulary system used jointly by his institution and four others in New York City, totalling 3,440 hospital beds. Among the points he cited were these:

- With 400 drugs listed, all but about 1 percent of drug needs can be satisfied.
- Appropriate prescribing information (therapeutic category, dosage forms, etc.) is provided for each drug under its generic name, and cross-indexed by brand name.
- There is an understanding among the hospital staffs that the pharmacy will substitute a generic for a brand-name product, but only when the pharmacy committee is convinced that clinical equivalency is assured.
- Although 12 percent of Montefiore's drug expense was for generic drugs, this amount accounted for 40 percent of all drugs provided. (*5*)

Another expert emphasized the role of the formulary in controlling drug costs, and indicated that formularies could be extended beyond hospitals to use by the out-of-hospital medical community:

> "This issue could be resolved, in part, by routine meetings between a committee of each county medical society with a counterpart committee from the local pharmacists. A semi-official formulary with enough flexibility to meet special situations could be devised. Care would be taken that marginal manufacturers not be included. I would visualize that both generic- and brand-name preparations be available, but that the physicians and pharmacists decide exactly where generic drugs may be included to best benefit patients. I believe that the physicians should then be supplied with a list of costs in his area so that he may prescribe wisely. In this way, it is hoped that confidence between the two groups may be established and that the patient will also gain more confidence in the professions that guard his health." (*26*, p. 730)

Such a project is now under joint development on a statewide basis by the Delaware Medical and Pharmacy Societies.

Textbooks

All widely used textbooks of medicine devote substantial space to considerations of drug therapy. Among these, one publication noted not only for its comprehensive scope of coverage but also for its convenience is the *Merck Manual of Diagnosis and Therapy*, published by Merck & Co. Now in its 11th edition, it includes therapeutic information with each disease description, and in addition provides a 183-page section on principles of drug therapy, drug formulas, and recommended dosages. The drugs included in this book are described by generic name only.

Industry Advertising

Of all the drug information sources available to physicians, perhaps none has been more sharply criticized than drug advertising. It has been variously described as costly, wasteful, misleading, slick, and undignified. It has also been termed educational, scientific, factual, up-to-date, and unique, in that it is required to present a balance of positive and negative information on each advertised product.

On two points at least, there is little argument—first, extraordinary amounts of money are spent to advertise drugs to prescribers; and second, through their prescribing of heavily advertised specialty products, the physicians give evidence of the success of these promotional efforts.

The drug industry makes no pretense that its advertising—in journals and by direct mail—is purely an educational device. The Pharmaceutical Advertising Club, an organization of some 650 members, stated in a recent position paper:

> "Good medical advertising sells drugs through the factual, accurate and timely presentation of information. Its function is to promote the use of a drug within its therapeutic potential for the alleviation of illness and to do so in accord with good medical and good business practices. In this sense it is informative as well as factual and accurate. Medical advertising cannot carry the responsibility of being, by itself, the educational vehicle whereby physicians learn of drugs." (*32*)

One prominent advertising agency official's feelings about the purpose of drug advertising are somewhat more direct:

> "Advertising is a selling force, not a postgraduate course in medical education. . . . First and foremost, the doctor is a human being. He wants to be fully informed, it's true, but when that information comes in the form of advertising he wants more from it. He wants his curiosity piqued, his imagination excited, his emotions stirred." *(13)*

Medical advertising, of course, consists of more than emotional stimulation. Under recently proposed FDA regulations, any advertisement which lists a clinical indication for a drug's use or contains a claim for safety or effectiveness must also present a brief summary of side effects, contraindications, warnings, hazards and precautions. The proposed regulations also require "fair balance" in the presentation of a drug's merits and its limitations.

The regulations state that "fair balance" is lacking, for example, if:

- Information is included in an advertisement that is not approved for inclusion in the package insert.
- Advantages are claimed for a drug without simultaneous disclosure of disadvantages.
- Obsolete information is used.
- Claims are exaggerated.
- Animal or laboratory data are cited as clinical experience.
- A statement by a recognized authority is used without also citing any unfavorable data from that authority.
- Statements are used out of context.
- Statistics are used in a misleading way.
- Headline or pictorial matter is misleading.

Under FDA's existing "fair balance" doctrine, complaints about the reliability and objectivity of direct mail and journal advertisements have become less frequent. The Commissioner of FDA said in recent testimony:

> "Senator, I may be an optimist, but I begin to feel that I am seeing some improvement in journal advertising. I look at these journals and I have greater difficulty in finding violative ads just on quick inspection. I think that the firms have a desire to improve their advertising. They believe that we are going to enforce the law and the regulations that were put out under the law. And this has been an important factor." *(17)*

Detail Men

Visits by company representatives to prescribing physicians represent the core of the drug industry's selling program—though usually no actual sales are made in the doctor's office. The functions of the medical detailer, as seen by the industry, are these:

- Inform the prescriber of newly available drugs.
- Provide detailed information on any of the company's products and, if necessary, obtain additional data from the company's home office staff.
- Provide the prescriber with educational materials of a general nature, some having nothing directly to do with the company's product line.
- Obtain information from the physician in order to provide the company with an assessment of its products by the medical community.

Despite the considerable cost of these visits ($7.69 per visit, in contrast to a 1 cent cost per reader of a typical drug advertisement), prescriber surveys have repeatedly demonstrated the importance of the detailer in facilitating drug selection. In a recent study of the assimilation of a new drug into the medical community, 57 percent of the 141 doctors queried revealed that the initial source of information about the drug was the detail man. (*8*, p. 53)

In another recent survey, 46 percent of Canadian respondents indicated that the detail man was "the most informative and/or most acceptable" type of drug promotion. *(12)*

In still another recent survey, Hagood and Owen reported:

> "Regarding the utility of the detail man, 85 percent of general practitioners gave him a strong vote of confidence, because his new drug information was valuable to them and he could order drugs directly for dispensing physicians. The other 15 percent felt that in view of the abundant available literature his services could be eliminated and the resultant savings passed on to the patient." *(20)*

The detailer was described by George Squibb, a former industry official, in Congressional testimony as the "best and most effective means of producing a sale or prescription . . ." He noted:

> "You understand the doctor is there often without information. He has not gotten it, either from his training or background, or he has not any time to get it any other way. The detail man

> moves into this situation with skill, with discretion generally speaking, and is a fine means, although expensive, of transmission of this information." (*38*)

The attitudes of practicing physicians as revealed in the surveys cited above, and of industry officials, stand in sharp contrast with the feelings of other clinicians and industry observers.

A physician at Georgetown University Medical Center described the detailer as follows:

> "He masquerades as an educator or, at least his parent firm stresses his role as a medical educator. He hopes to ingratiate himself to the physician by providing him with scientific information, albeit somewhat biased, regarding the products of his employer, by leaving samples of his product to help the patients or the physician use the product in question. He will graciously offer to fill the physician's family needs with his employer's product before taking his leave. If the physician is busy, as most are, and gets a thumbnail resumé of the new product purportedly better than other similar products he has used, he may well try it. He has the starter samples available so that he can somewhat reduce the cost of the drug to the patient, not to mention the fact that by handing out these samples he gains further good will from the patient, and a prescription for the drug is a natural byproduct." (*37*)

Drug Samples

Most large manufacturers distribute samples of drugs without charge to physicians—particularly drugs which are new to the market. Sample distribution is designed to help the physician make a personal determination about the utility of the product, and to provide the patient with a few initial doses of a drug before a prescription can be filled. Moreover, in the case of some drugs, they provide the physician with a ready supply of the drug for distribution in an emergency situation or when pharmaceutical services may not be readily available.

Sample distribution also has some drawbacks. Margaret Kreig has documented some of the dangers. (*25*) Among them she cites the possibility that since few doctors can use all of the samples sent to them, office aides may give or even sell them to an intermediary, from whom they may reach the black market. Samples intended by physicians for use in charity or educational institutions have been diverted for drug abuse by students and others.

Postgraduate Education

Many medical schools and other institutions provide continuing education programs for physicians, and some of these include current information on drug therapy. Such programs, however, reach only a small proportion of physicians in practice, and their overall quality has been questioned. (*7*, p. 573; *21*, p. 749) Few of them are specifically directed to the broad principles of drug evaluation, comparison, selection and use, and to the key socioeconomic issues involved.

One pharmacologist who himself conducts a continuing drug education program for physicians has written:

> ". . . efforts in postgraduate education in pharmacotherapeutics should be further supported and greatly expanded. I am referring to such activities as clinical pharmacology seminars, symposia, teaching rounds, and lectures not just in the major academic centers but at all hospitals and medical societies throughout the country. Much more could be done in this area if more financial support and qualified teaching personnel were available." (*24*)

The possibility of developing and extending new approaches to continuing education about drug therapy is to be considered at a conference of leading clinicians and pharmacologists to be held early in 1969 under the sponsorship of the National Academy of Sciences-National Research Council. A number of experimental approaches and the means by which these approaches may be evaluated will be discussed.

Industry Support for Postgraduate Education.—Nearly every major drug manufacturer has contributed to the support of symposia, conferences, and other forms of education relating to drug therapy. Some of these are concerned with a specific product being introduced or marketed by the manufacturer; others cover a broader range of subject material.

Some pharmaceutical companies also contribute substantially to the support of formal postgraduate training in basic and clinical pharmacology, often through the establishment of nonprofit foundations. In the 12-year period, 1953–64, for example, the Smith Kline and French Foundation contributed more than $7 million for support of pharmacology programs and for the unrestricted support of other medical education programs. The Burroughs Wellcome Fund provides 5-year awards for the training of clinical pharmacologists, each in the amount of $100,000, payable during the period of the award. To date, 15 Burroughs Wellcome Scholars have been recipients of the award.

As a group, the manufacturers support the Pharmaceutical Manufacturers Association Foundation. The PMAF, founded in 1965, has as its stated aim: "support of fundamental research in drug toxicology, and support of programs of research and training for personnel in clinical pharmacology and drug evaluation." (*34*)

Since 1966, the PMAF has provided annual Faculty Development Awards in Clinical Pharmacology. The awards, which are granted for a 2- or 3-year period, are made directly to medical schools on behalf of the successful applicants. The level of support is keyed to the institution's existing salary structure. Six grantees have been selected since establishment of the awards.

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PART B

DRUG QUALITY

Chapter 4

INTRODUCTION

During the past half century, and especially during the past three decades, much attention has been directed to the value of drugs, and their safety and efficacy. More recently, attention has been focused on drug quality in general and clinical equivalency in particular.

The issue of clinical equivalency is this:

Given two drug products containing essentially the same amount of the same active ingredient in the same dosage form—that is, two chemical equivalents—will they produce essentially the same clinical effects?

On the answer—or answers—depend medical and economic decisions of considerable importance.

If the physician can be given reasonable assurance that two such competitive products will, in fact, give predictably equivalent clinical effects, then his choice between the two may well be based on relative costs. Under such conditions, there would be little justification for prescribing a relatively expensive brand of a drug when an equally effective counterpart is available at substantially lower cost.

But if the physician cannot be given this assurance, his clinical judgment would dictate that he use only the product which can be expected to yield the desired clinical effects—regardless of cost or any other nonmedical factor.

In attempts to find answers and develop policies which will lead to desirable economic savings, without lowering the quality of medical care, it has been held that the only crucial factor is whether or not the product in question can meet all official standards. If two tablets, for example, both meet the specifications for identity, strength, quality, and purity published in the official standards, it has been proposed, then—regardless of any other factors—they will assuredly yield identical clinical results.

Experts on drug standards and controls have stated repeatedly that, on the basis of available evidence, for the vast majority of drugs, this assumption is indeed correct. But the fallibility of existing standards has been shown by the finding—in rare cases—that different physiological effects can be produced by two different products, each formulated by a different manufacturer but both conforming to the same official specifications.

The answer to the question posed above thus must be:

Given two drug products containing essentially the same amount of the same active ingredient, the two products may not in all cases produce the same clinical effects.

This, however, is only a partial answer. It is still essential to determine how often this lack of clinical equivalency is likely to occur, which drug products are involved, what factors are responsible, and what steps should be taken to correct the situation.

It seems evident that no acceptable solution can be achieved by any simple, sweeping generalization. Instead, an appreciation of the complexities of drug quality requires consideration of the factors involved in clinical equivalency and in biological equivalency, the nature and relative merit of existing official drug standards, and the establishment and enforcement of quality control regulations.

Chapter 5

CLINICAL EQUIVALENCY

The question of clinical equivalency—the reproducibility of effectiveness among drug products containing the same active ingredients—is scarcely new. It has been put to pharmacologists, physicians, drug makers, and others with increasing vigor since the first medicines were brought to colonial America.

In 1789, soon after the Federal Constitution had been ratified, a group of physicians in Philadelphia circularized their colleagues in the newly ordered States, pointing out "the absolute necessity of some standard amongst ourselves to prevent that uncertainty and irregularity which in our present situation must infallibly attend on the compositions of the apothecary and the prescription of the physician." (*23*)

During the 18th and 19th centuries, and into the 20th, the "uncertainty" among physicians was related to: (1) drug adulteration, misbranding, the substitution of one active ingredient for another, or the dispensing of products in which the active ingredient was present in too small or too large amounts, causing gross drug failure or unexpected toxic reactions; and (2) the lack of basic pharmacological knowledge.

This kind of uncertainty has been largely dissipated. Most drug manufacturers have exerted great effort to develop and maintain high standards of drug production and quality control. There has been almost a century and a half of meticulous research, deliberate judgment, and response to new knowledge by such official standard-setting compendia as the *U.S. Pharmacopeia* and the *National Formulary*. There have been progressive increases in Federal responsibility and authority to govern the safety and efficacy of drugs, and to oversee the efforts of manufacturers to develop and maintain high standards of drug production and quality control.

As a result, instances of gross drug failure and unexpected toxic results have become increasingly infrequent.

The question of drug quality, however, remains a critical matter, but now it is related not only to safety and efficacy but also to the relative efficacy of chemical equivalents. This change in emphasis has stemmed in considerable part from two developments which are closely linked with patterns of drug marketing:

- With the expiration of patents on some widely used drugs sold for many years under a brand name, low-cost chemical equivalents appeared on the market in increasing volume.
- With the increasing role of the Federal Government and many State governments as purchasing or reimbursing agents for drugs, and the possibility that this role may be expanded even further, there has been mounting insistence that government drug programs be based on the use of low-cost chemical equivalents wherever possible and consistent with high quality of medical care.

The responses to these developments have been markedly diverse.

On the one hand, as noted particularly during recent Congressional hearings,[1] [2] it has been claimed that the use of low-cost chemical equivalents is both economically justified and consistent with high quality care. On the other, representatives of major brand-name manufacturers have claimed that such use of low-cost chemical equivalents may have economic justifications, but it is clearly inconsistent with high quality care.

Advocates of low-cost generics have noted that their products must meet USP or NF specifications, and therefore are clinically or therapeutically equivalent by definition. Their opponents have stated that these standards may not be set high enough, that strict quality and process controls within a manufacturer's plant are more important, and that the low-cost generics cannot be accepted as clinically equivalent.

An important element in this controversy has been the claim of superior quality controls by the major brand-name manufacturers, and the communication of that claim—through advertising, direct-mail operations, and the visits of detail men—to the practicing physician. One view of the result has been presented by a Harvard economist:

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[1] Hearings before the Committee on Finance, U.S. Senate, on H.R. 12080, 1967 (the Long Hearings).

[2] Hearings before the Subcommittee on Monopoly of the Select Committee on Small Business, U.S. Senate (*28*) (the Nelson Hearings).

> "When doctors are forced to choose between different chemical compounds which purportedly do the same thing, a large measure of uncertainty is certain to exist. Even though a doctor might believe that different compounds have similar therapeutic effects, he is never quite sure, and the prudent course of action is to prescribe the drug which has become well-known. And becoming well-known is, of course, the function among other things of the level of advertising and promotional expenditures. . . . Even in the absence of chemical differences among products, however, considerable uncertainty remains as to whether different brands are equally good." *(4)*

Industry officials, clinicians, researchers and trade analysts seem to agree on one point: significant changes in public policy, significant changes in governmental drug programs, significant changes in the regulations of drug manufacture, significant changes in drug standards, and, in response to these, significant changes in marketing strategy—all of these hinge upon resolution of the complex problems involved in clinical equivalency.

On the scientific issues, there appears to be less agreement—in large part because the direct comparison of clinical equivalency seems to be impractical at this time.

Clinical and Biological Equivalency

For the direct determination of clinical equivalency, the ideal method would be the comparison of two or more drug products, containing the same active ingredients, in the same tablet or capsule or other dosage form, in the same amounts, and measurement of their relative effects in human patients in the alleviation of symptoms or the control of a specific disease.

Except perhaps in rare instances, such a comparison is impractical. It would be time-consuming and costly. It would be complicated not only by human differences but by differences in the symptoms or diseases under consideration. Furthermore, it would involve human experimentation under conditions in which an unexpected lack of clinical equivalency might well have serious adverse results.

Instead, attention has been directed to the use of *biological equivalency*—or relative physiological availability—measured in normal subjects as a proxy for the direct measurement and comparison of clinical effects.

This is based on the general agreement among pharmacologists that in the case of most drugs—certainly those taken orally for their effects in the blood, the liver, the brain, or other internal organs—their therapeutic effectiveness will be substantially related to the absorption of the active ingredient into the blood stream. Thus, if two preparations yield the same blood concentration of active ingredients, they will presumably yield the same therapeutic effect. *(5)*

Factors in Biological Equivalency

For a drug[3] to produce its expected therapeutic effect, it must be:

- present in the tablet or other dosage form in the required concentration;
- released from the dosage form and, in the case of most solid forms, disintegrated into residual granules;
- dissolved within a reasonable period of time; and
- absorbed and delivered to the sites of action in a concentration adequate to produce the desired effect.

Once the active drug has been absorbed, such factors as protein binding, metabolic fate, and excretion are generally predetermined by the nature of the drug itself, and not by any differences which may have been concerned in its manufacture.

Physiological availability varies widely with different dosage forms. A drug in liquid solution, for example, has bypassed the rate-limiting processes of disintegration and dissolution and is more rapidly absorbed than the same drug presented in capsule or tablet form. Similarly, a tablet in coated form tends to be absorbed more slowly than one which is uncoated.

The salt or ester form of the active ingredient may also have an influence upon its absorption. Ephedrine, commonly used in respiratory disorders, is available as both the sulfate and the hydrochloride. Although both are produced in capsules of the same strength, and may be assayed for ephedrine content alone, they have different physical properties and are regarded as different drugs.

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[3] This discussion will be confined to orally-administered solid forms, in which formulation problems appear to be the most significant.

It is important that measurements of clinical equivalency reflect these considerations, and that comparative studies be confined to strictly comparable dosage forms.

Formulation Factors

Among comparable dosage forms, a number of formulation factors can and do have distinct effects upon measurements of physiological availability.

Solubility.—Once a drug is dissolved in the gastrointestinal fluid, absorption is usually rapid. Dissolution of the drug, however, is not only a prerequisite: it is generally the rate-limiting step in the absorption process. It is not surprising, therefore, that instances of clinical nonequivalency are most frequent among drugs of inherently low solubility. The Director of the *National Formulary*, has written:

> "In our past consideration of the problem of physiological availability of drugs, information coming to the *National Formulary* office has indicated that only in the case of rather insoluble drugs do we encounter any difficulty in correlating in vivo test results with in vitro test results. . . . The principal problems of physiological availability—and specifically of lack of correlation between present laboratory methods when compared with in vivo or clinical tests—appear to be limited to the drugs which have a water-solubility of less than one percent." (*7*)

These observations have been confirmed by others. (*9, 12, 15*)

Particle Size.—For drugs of high solubility, the disintegrated granules pass rapidly into solution, and particle size or surface area is of limited importance. In the case of low solubility drugs, however, particle size is critical. This has been well documented in the case of griseofulvin, a highly insoluble antifungal agent. By reducing the average particle size from a diameter of 10 to 2.7 microns, the effective dose can be reduced by half, with both preparations yielding nearly identical blood levels. (*1*)

Crystal Form.—Some drugs may exist in more than one crystal structure, a property known as *polymorphism*. This is true, for example, of several barbituric acid derivatives and steroid hormones. Often the dissolution rate will vary significantly among polymorphs, the most stable form being the least soluble, and with a tendency for others to revert to that form. A polymorph which reverts at a slow rate to the stable form is called "metastable" and, because of its enhanced solubility, is of particular interest to drug manufacturers. The amorphous (i.e., noncrystalline) forms of substances such as chloramphenicol palmitate, for example, may have higher dissolution rates and produce more rapid and higher blood levels than corresponding crystalline forms.

Tablet Compression.—Pressure exerted in the tableting process is another important factor in disintegration and dissolution of tablets. Overcompression may result in the fusion of particles and in delayed or incomplete absorption.

Adjuvants.—A variety of agents may be added to the active ingredient in the production of a finished dosage form. Among them are:

- substances which promote disintegration of the dosage form on contact with gastrointestinal fluids;
- fillers, to provide additional bulk to a product containing a small amount of active ingredient:
- lubricants, to facilitate the tableting process:
- binders, to assure that the product remains in a cohesive form until ingested: and
- coatings, flavorings, and colorings.

All of these substances must be selected with knowledge of the ways in which physiologically inert substances can react with active ingredients. In some cases, notably among tetracycline antibiotics, unanticipated interaction of inert ingredients with the active principle has resulted in reduced absorption. (*18*)

Age.—Changes which some products may undergo during prolonged storage, especially under severe climatic conditions, can result in physical and chemical alterations which will affect absorption.

Chapter 6

DRUG STANDARDS

The factors involved in determining physiological availability, as well as the formulation factors involved in drug production, have become important elements in the current serious reappraisal of the role and status of official drug compendia.

In the United States, the two most important compendia are the *U.S. Pharmacopeia* (USP) and the *National Formulary* (NF).[1] They contain drug standards and specifications which were presumed to assure clinical equivalency of chemically equivalent drugs, high cost or low cost.

Whether or not their current standards are adequate to assure this equivalency has now been questioned, not only by industrial representatives—who may have much to gain or lose by maintaining or changing those standards—but also by many independent scientists and clinicians. (*12*)

The USP and the NF both have long and distinguished histories. In 1906, when the first Federal Food and Drug Law was enacted, giving them official status, the USP had already served as a source of drug standards for 86 years. Both publications have been guided by objectives set down originally by the USP in 1820:

> "It is the object of a Pharmacopoeia to select from among substances which possess medicinal power, those the utility of which is most fully established and best understood; and to form from them preparations and compositions, in which their powers may be exerted to the greatest advantage. I should likewise distinguish those articles by convenient and definite names, such as may prevent trouble or uncertainty in the intercourse of physicians and apothecaries.
>
> "The value of a Pharmacopoeia depends upon the fidelity with which it conforms to the best state of medical knowledge of the day. Its usefulness depends upon the sanction it receives from the medical community and the public; and the extent to which it governs the language and practice of those for whose use it is intended." (*20*)

In the Food, Drug, and Cosmetic Act, the USP and the NF are charged with providing uniform standards of strength, quality, and purity. For nearly a century and a half, the enormous task of revising standards was accomplished in an atmosphere of quiet reflection that attracted little public notice.

The quietude was first broken in 1959. Since the Kefauver hearings, which began that year, questions have been raised about the relative quality and efficacy of brand-name drugs and their low-cost generic counterparts, and the adequacy of existing official standards.

Compendia Standards

The makeup of the USP and the NF is roughly the same. Both include detailed monographs of standards, tolerances, and specifications on each listed drug and dosage form; the applicable tests to determine compliance with the standards and specifications, and procedures for assay: a section describing test procedures of more general application; specifications for various reagents; and other supporting data.

Drug Monographs.—Although the standards vary considerably, certain tests are specified for nearly all solid dosage forms. These include:

- Identification: For each drug a qualitative or semiquantitative method of identification is provided.
- Assay: A specific number of tablets or capsules, generally 20, is reduced to powder form, and analysed for drug content. Limits of mean drug content are provided for each product, but this test in itself does not necessarily assure uniform composition of all tablets.
- Weight Variation: This is likewise an indirect measure of content uniformity. For example, the mean weight of 20 tablets is calculated. Not more than two tablets may vary from the mean beyond specified limits, which become narrower with increasing tablet weight. No single tablet may fall outside more than twice the percentage tolerance at any given tablet weight.
- Content Uniformity: For certain critical drugs, 10 tablets or capsules are assayed individu-

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[1] These and other formularies are discussed elsewhere. See page 43.

ally. If a single unit contains less than 85 percent or more than 115 percent of the average of the tolerance limits provided for the product, then 20 more units must be tested. The test is failed if more than one unit falls outside of the 85–115 percent range. This test is a very recent innovation, appearing initially in the compendia in 1965. Such a requirement has become technically feasible only in recent years as a result of great strides in microanalysis.

- Disintegration Test: This procedure, introduced only in 1950, represented the first attempt by the compendia to provide some measure of physiological availability. It is based on the obvious assumption that a drug which has not disintegrated into residual granules cannot be dissolved or absorbed. The procedure is straightforward. Six tablets are placed in a special device and immersed in gastric fluid or other specified test fluid. The tablets must disintegrate into particles small enough to pass through a fine mesh screen within a specified time. If one or two of the tablets fail, then an additional 12 are tested. The entire test fails if more than two tablets are not fully disintegrated.

- Foreign Substances: For certain drugs, limits are established for the presence of related but undesirable substances. Aspirin tablets, for example, must not contain more than a specified amount of free salicylic acid. Similar limits are placed upon the presence of foreign steroids in tablets of prednisone, a corticosteroid hormone derivative. In addition to these tests which apply specifically to the drug dosage form, monographs of standards and specifications are provided for the various individual bulk ingredients which are utilized in preparing the dosage form.

Adequacy of Compendia Standards

The value of compendia standards to settle all matters of clinical equivalency, or biological equivalency, and related problems has been the focus of much debate.

Manufacturers of low-cost chemical equivalents, whose products must meet USP and NF requirements, have presented the view that their products—by meeting these compendia requirements—are therefore clinically or biologically equivalent to more expensive brand-name products.

In turn, the manufacturers of most costly brand-name products have expressed the opinion that conformity to USP and NF requirements is only one essential. Application of good manufacturing techniques and rigid quality controls may be at least equally important. They have repeatedly urged that no governmental regulations be established which, directly or indirectly, should induce a physician to prescribe a low-cost chemical equivalent.

When two generic equivalents are available at different prices, they have emphasized, the physician must, in the last analysis, rely on his knowledge of the manufacturer's ability to make drugs of high and uniform quality.

In general, the questions raised about compendium standards are these:

1. Dose conformity with existing USP and NF standards assure clinical or physiological equivalency?

2. Can the official standards be revised swiftly enough to reflect new developments in the pharmaceutical sciences?

3. Considering the accumulation of knowledge and experience during 62 years of Federal drug control, is it still reasonable to have official standards established by private organizations?

Assurance of Equivalency.—In numerous conferences held by the Task Force, as in many Congressional hearings, hope was expressed that scientific support could be found to justify one of two alternative conclusions: (a) all generic drug products meeting USP and NF standards can be considered clinically or biologically equivalent, or (b) no such drugs, merely because they conform to existing USP and NF standards, can be considered equivalent.

On this subject, the Task Force has found full agreement among informed scientists and clinicians:

> "The existing standards do not provide *complete* assurance of clinical or biological equivalency."

Well-documented examples of nonequivalency (as measured by physiological availability) among drugs meeting official standards do exist and have been reported. (*12*)

The Director of the *National Formulary*, however, has expressed the opinion that not many instances of this kind should be expected. He has claimed that physical, chemical, and pharmaceutical standards are more precise and reproducible than are clinical methods; and that drug standards can serve in most cases as an indirect measurement of drug effectiveness.

> "Information available in the published literature reveals only isolated case histories, and very few scientifically performed studies, which demonstrate substantial differences in 'therapeutic equivalence' between two comparable drug products—also referred to as generic or brand equivalence. Consequently, while we must recognize that this factor exists, currently available evidence indicates that only very seldom is there a difference in clinical performance if the official compendia standards are met by both drug products."

He added:

> "I would say that I would be hard pressed to name more than even a few—less than five—well-conducted, clinically acceptable studies which have demonstrated significant differences between two or more products clinically where they have met all of the chemical and physical standards as provided by the official compendia." (*8*)

The foregoing position is in general accord with that of representatives of the USP, of the Commissioner of FDA, and of a number of pharmacologists who have testified before Congress. (*19*) They have indicated that, by and large, the standards in the USP and the NF are adequate, and that these can and will be improved to provide better standards for the few drugs in which equivalency has been questioned.

In contrast, those who are skeptical about the general existence of therapeutic equivalency—a view held by many (but not all) brand-name drug manufacturers—have presented contrary views:

1. They assert that the technical literature is replete with instances of nonequivalency among drugs meeting official standards. On November 29, 1967, a quality control official of Smith Kline and French presented to the Senate Subcommittee on Monopoly a document containing 211 references to the influence of formulation factors on therapeutic equivalency, and several review articles of a more general nature. It was claimed that many of the articles referred to clinical studies describing nonequivalency. (*21*) [2]

2. They feel that the number of reported instances of nonequivalency understates the problem because this branch of pharmaceutical science is new and relatively unexplored. In testimony before Senator Gaylord Nelson, Joseph Stetler of the Pharmaceutical Manufacturers Association declared:

> ". . . the burden has always been shifted to the proof of lack of equivalence. Nobody has come up with proof of equivalency. This is a very spurious assumption that is made because USP has standards. Whether or not they exist, whether or not they are followed, and what they mean in the final analysis in terms of therapeutic effectiveness is still a question."

Then he added:

> ". . . the important thing which cannot be forgotten is that there is not absolute proof of effectiveness for the 3,000 products. There is lack of proof of therapeutic equivalence for many or most of those products. It is a question of where the burden of proof lies in this matter." (*24*)

3. The manufacturers and many independent pharmaceutical chemists point to the elaborate quality control systems that operate in the research-oriented firms. In many cases, they report, their testing of raw materials and final products goes far beyond compendia specifications in terms of both numbers of checks and limits of tolerance.

The dispute in this broad area cannot be resolved by determining whether *all* chemical equivalents meeting official standards can *always* be assumed to be therapeutically equivalent, or *never* be assumed to be therapeutically equivalent.

From the available scientific data, the following points seem evident:

- Although few cases of nonequivalency have been documented, they cannot be ignored. Each may represent a threat to the health or life of many individuals.
- In the same way, the importance of nonequivalency should not be overexaggerated in establishing the extent of the problem. Among the most widely-used prescription drugs, about 80 percent are still under patent, or otherwise available from only a single source, with no low-cost generic products available, and in their case the question of equivalency does not arise.
- Among the remaining 20 percent, for which low-cost chemical equivalents are on the market, some are drugs which are seldom if ever needed

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[2] On March 5, 1968, Senator Gaylord Nelson, chairman of the subcommittee, sent this document to Dr. Edward G. Feldmann of the *National Formulary*, who stated in a detailed reply that the number of valid reports of nonequivalency in the document was probably smaller than five.

for serious or critical illness, and for which exact equivalency does not appear to have major clinical importance. Some are highly soluble drugs which—on the basis of present knowledge—would be expected to be absorbed rapidly into the blood, and would therefore be expected to offer no significant problems of physiological availability. The others—those required for serious illnesses, with a need for precisely predictable absorption rates, and with relatively low solubility—are the ones which would seem to call for particular study under controlled, scientific conditions.

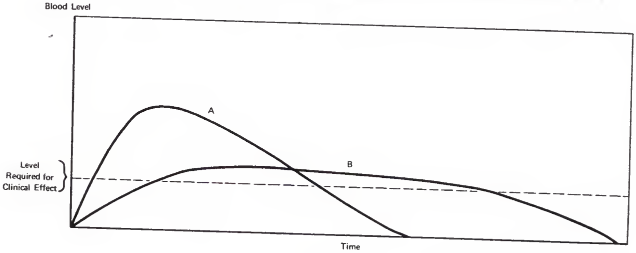
- Due consideration should be given to the possibility that lack of equivalency is more frequent than reported.
- Consideration should be given to the possibility that two chemical equivalents may produce quite different absorption rates, and might therefore prove to be nonequivalent therapeutically, but both might nonetheless have therapeutic value. For example, drug A might give a rapid absorption, a high peak, and a rapid decrease in blood levels, while its chemical equivalent B might give a slower absorption, a lower peak, and a relatively extended presence in the body (Figure 1).[3] Under such conditions, the two generic products might both be made available—presumably under different names and labels—to the physician, for such use as his clinical judgment might dictate.
- Consideration should be given to raising all USP and NF standards in general, and specifically for those drugs in which lack of biological or clinical equivalency has been demonstrated or suspected.
- Consideration should likewise be given to the possibility that certain generic counterparts may be equivalent in their absorption rates but differ in producing such side effects as unpalatability which may interfere with patient acceptance of the prescription.

Changes in Standards.—A spokesman for the Pharmaceutical Manufacturers Association has stated:

> ". . . The USP does a fine job as far as they have gone. They recognize, as we recognize, that there probably should be other standards developed, and they are now being developed, with the cooperation of the manufacturers.
>
> "What we say on USP standards is not intended at all to be critical of that book, and it is not. But USP is not the whole answer.
>
> "There are other standards, and they are being revised now. When those are in the book, USP standards will mean more than they mean now. Whether they will ever answer completely the problem, I cannot say." (*24*, p. 1373)

The compendia officials have stood in defense of their standards. They admit to a conservative approach in the admission of new articles and in the revision of standards. They point out that there is no room for misjudgment—that these standards have the force of law immediately upon publication; that the specifications apply not to a single manufacturer, but to all manufacturers and to

Figure 1.—Hypothetical Blood Level Curves for "High Peak" (A) and "Low Peak" (B) Products



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[3] Whether or not such a difference between chemical equivalents does actually occur with modern prescription drugs has not been clearly established. Such differences, however, have been found to occur with ethyl alcohol in the form of different alcoholic beverages. (14)

countless independent testing laboratories; that the judgments are not unilateral but reflect the best thinking of independent researchers and industrial chemists, and that the harvesting of these judgments and the reconciliation of differences in an orderly manner is time consuming.

Despite these problems, they maintain, the standards do reflect new developments. The revision committees do not wait until the quintennial revision to introduce new specifications. The USP, for example, publishes revision announcements at an average rate of two a year. The announcements are published cumulatively in the USP supplement which is distributed twice during each 5-year revision period. NF supplements have been issued with comparable frequency.

As examples of the sensitivity to new developments that characterizes the revision process, compendia officials cite the following recent developments:

1. The disintegration test, the first official indicator of physiological availability, introduced in 1950, has been substantially modified for most drugs. In the 1960 revision of USP and the 1965 revision of NF, over half the tablets had distintegration time limits reduced, most by at least 50 percent.

2. The content uniformity test, introduced in the 1965 revisions of both compendia, will be extended in the revision now in preparation to include all listed tablet forms containing 50 milligrams or less of active ingredient.

3. Specifications governing particle size will be applied to more drugs in which this factor has been shown to be critical.

Examples demonstrating the influence of this formulation factor upon physiological availability have been cited in this chapter. In some cases, notably the oral antifungal agent griseofulvin, the compendia have introduced a particle size specification. The USP and the NF are working with appropriate study sections of the American Pharmaceutical Association and the Pharmaceutical Manufacturers Association to develop methods for the standardization and control of these factors.

4. A dissolution rate standard will be introduced for the first time in the 1970 revisions of USP and NF.

This action derives from the observation that the gastrointestinal absorption and physiological availability of drugs is closely related to the rate at which the disintegrated particles pass into solution. Appropriate methodology in this field has been difficult to attain. Two important projects begun in 1967, however, have accelerated the flow of information that has lead to a judgment about the utility of dissolution as an appropriate standard. First, the USP and the NF have formed a joint panel on physiological availability to make a comprehensive review of past and projected studies. Second, the Task Force on Prescription Drugs has undertaken to coordinate a number of clinical studies sponsored by the FDA and the Public Health Service which, it is hoped, will provide additional new information.[4]

5. Expiration dates will be applied to additional drugs in which stability has been a troublesome factor.

6. The number of drugs covered by compendia monographs will be substantially increased in the 1970 publications. The USP will be enlarged from 915 to 1128 articles and the NF from 815 to 1041.

Several of the foregoing steps have been taken by cooperation among representatives of USP, NF, industry, and Federal agencies. Additional proposals, under consideration by these various representatives working in cooperation with the Task Force on Prescription Drugs, include these:

1. *Introduction of a clinical test standard.*—Inclusion of a requirement to supply data based on animal or human studies would not be unprecedented. Clinical test standards for liver extract in the treatment of pernicious anemia were published in the USP from 1938 until 1952, when spectrochemical methods for the determination of the active principle, Vitamin B_{12}, were introduced. (*13*) Acceptable clinical standards might be blood concentration or urinary excretion curves using, as the reference material, a formulation of the drug which has been proven therapeutically effective. In many cases, this could be the formulation upon which the FDA "New Drug Application" (which is described further in this chapter) was based.

2. *Formula specifications.*—Some formulation factors that can affect therapeutic equivalency have been pointed out above. An alternative solution is for the official compendia, among specifications for drugs in which formulation is both critical and especially difficult, to include an exact formula—one which has been shown therapeutically effective. Similar formula specifications could be provided

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[4] See page 39.

in the case of certifiable drugs and "new drugs" which are not included in the official compendia but are controlled by the FDA. Such a move might require an appropriate amendment of the Food, Drug, and Cosmetic Act. A number of drugs, however, are neither certifiable, listed in the compendia, nor subject to "new drug" procedures. For these, new legislation would also be required.

Public Versus Private Compendia

The major drug compendia—notably the USP and the NF—were in existence in 1906, when Congress faced the need for yardsticks of purity and strength for the new food and drug law. It was not surprising that the legislators turned to these existing compendia for the requisite tests and standards.

Congress has since brought about significant changes by which the FDA and the PHS Division of Biologics Standards have been given increased authority not only to enforce drug standards, but to create them. This is true for antibiotics and biologicals, both of which—in addition to insulin—are subject to batch certification by the appropriate regulatory agencies.

Some have advanced arguments for Federal testing of *all* drugs. The Chief of the Gastrointestinal Research Section of the Georgetown University Medical Center in Washington supported the idea in testimony before the Nelson Committee. "I would most definitely consider it both worthwhile and in the public interest," he said. (*22*) He conceded, however, that this position was not shared by most of his colleagues.

Most private and government officials are quite prepared to argue that the compendia have more than adequately fulfilled the role assigned to them in the original Food and Drug Act and in all of its revisions. The most optimistic of these envision a time when the combination of more widespread in-plant controls and more effective field surveillance will make even the present government certification superfluous.

Chapter 7

QUALITY CONTROL

Role of Industry

Traditionally it is said in the drug industry that drug standards cannot build quality into a product—only the manufacturer can do that. And, it might be added, only the manufacturer can build therapeutic efficacy and equivalency into his product.

Traditionally, too, some manufacturers—through a pride in craftsmanship and a strong sense of responsibility—have sought to employ the best possible quality control methods. Some of them have developed and followed their own standards and specifications which were sometimes even more rigid than those established by the official compendia.

Not all drug makers, however, have gone to such trouble. Some of these—perhaps with a lower degree of responsibility and a higher interest in profits—have utilized shoddy manufacturing practices and careless control testing. Their products were often undependable in composition, sometimes adulterated, and frequently misbranded.

To protect the public against such hazards, the Federal Government determined more than 60 years ago that it had the responsibility of regulating the quality of drug products and upgrading manufacturing practices. Acceptance of this responsibility was marked by the enactment of a series of far-reaching laws involving a number of Federal agencies, and especially what is now the Food and Drug Administration.

Federal Drug Legislation

Stemming from the public disclosure of scandalous adulteration, contamination and misbranding of foods and drug products, the first Federal Food and Drugs Act was enacted by Congress on June 23, 1906, and signed into law by President Theodore Roosevelt a week later. The act was not revolutionary, nor even new to Congress. At least a dozen States already had some surveillance authority, and more than 100 bills had been introduced at the Federal level during the previous three decades.

The act prohibited interstate shipment of adulterated or misbranded foods and drugs. Adulterated drugs were defined as medications differing in strength, quality, or purity from the standards laid down in the USP or NF—which were designated as official compendia—but manufacturers could depart from those standards if they chose to put their own statement of strength, purity or quality on the label. Misbranding was defined to include any "false or misleading" statement or graphic representation on the label.

The courts subsequently held that the misbranding definition did not apply to therapeutic claims. Congress responded to that interpretation with the enactment in 1912 of the Sherley Amendment, which prohibited labeling of medicines with false and fraudulent therapeutic claims.

The 1938 Act.—During the Franklin D. Roosevelt administration, legislation was drafted to expand greatly the government's role in the regulation of foods, drugs, and cosmetics.

In part, it was designed to overcome shortcomings in the 1906 Act. The final thrust toward its enactment came from the "elixir of sulfanilamide" affair—a tragic event in which a drug maker dissolved the new wonder drug, sulfanilamide, in toxic di-ethylene glycol, and marketed it without testing it for safety. Before its hazard was recognized, the elixir took the lives of 107 victims, most of them children.

The Food, Drug, and Cosmetic Act of 1938 provided safeguards against repetition of the "elixir of sulfanilamide" tragedy. It included a provision that "prohibits traffic in new drugs unless such drugs have been adequately tested to show that they are safe for use under the conditions of use prescribed in their labels."

Other provisions strengthening the regulation of drugs included the authorization to carry out factory inspections and the addition of the court injunction as an enforcement tool.

In signing the act, President Roosevelt said:

> "No honest enterpriser need fear that because of the passage of such a measure he will be unfairly treated. He would be asked to do no more than he now holds himself out to do. It would

merely make certain that those who are less scrupulous than I know most of our producers to be cannot force their more honest competition into dishonorable ways." (*6*)

The 1938 Act is still the basic statute for drug regulatory control in the United States, but it has been amended several times through the years as Congress recognized additional consumer protection needs.

Major Amendments.—In 1945, the act was amended to require certification, on a batch-by-batch basis, of the safety and potency of penicillin products. Later amendments extended this requirement to other antibiotics. The Durham-Humphrey amendment, enacted in 1951, required that drugs which cannot be safely used without medical supervision be dispensed only upon prescription and bear the Rx legend. In 1960, the Color Additive amendments were passed, authorizing FDA to set safe limits on the colors used in drugs, as well as in foods and cosmetics.

The Kefauver-Harris drug amendments of 1962, however, brought the most significant changes in the 1938 Act. Enacted in the wake of the thalidomide tragedy in Europe, the amendments provided that new drugs should be evaluated for effectiveness, as well as for safety, before they are cleared for the market. The FDA was authorized to monitor the results of clinical trials of investigational drugs. Before starting clinical trials, manufacturers must submit reports of preclinical tests, including animal tests, and other information adequate to justify the proposed clinical testing. The amendments also require manufacturers to report promptly to FDA any adverse effects and other clinical experience concerning the safety and effectiveness of a drug or antibiotic already on the market.

Other provisions of the amendments strengthened FDA's factory inspection authority and authorized FDA to issue good manufacturing practices regulations to assure adequate quality controls in drug plants. FDA was given the responsibility for the regulation of prescription drug advertising. The amendments stipulated that new drugs may not be cleared for marketing if the labeling is in any way false or misleading.

In addition to requiring evidence of the effectiveness of new drugs marketed since 1962, the amendments authorized review of the efficacy of new drugs which had been cleared only for safety since 1938. The National Academy of Sciences-National Research Council began the review of some 3,000 drugs in mid-1966 under contract with the FDA.[1]

FDA Activities

The responsibility of FDA to oversee the flow of drugs through interstate commerce—and, under certain conditions, in intrastate commerce—is implemented in four major areas: plant inspection, product surveillance, premarketing clearance of new drugs, and certification of insulin and antibiotics.

Plant Inspection.—At first, FDA inspectors could examine drugs only after they had reached the market, but had no authority to inspect and approve the conditions under which they were produced.

The first chief inspector under the 1906 law realized, however, that sampling drugs in the marketplace would not suffice. A more prudent course, he reasoned, would be to identify and correct drug defects as close as possible to the source. By 1910, a training program in plant inspection had been organized and systematic inspections of facilities and processes begun to determine the likelihood of violations.

Definitive authority for plant inspection was granted in the 1938 law, and expanded in 1962. The law now requires that each manufacturer be registered with the FDA and that each plant be inspected at intervals of not less than 2 years.

At present, FDA inspectors are required to complete a 3-week course at the University of Rhode Island (soon to be extended) to acquaint them with a basic knowledge of pharmacy and drug manufacturing. A more advanced course, given at the University of Pittsburgh and at FDA's Washington headquarters, further qualifies inspectors to monitor investigational drug studies and to follow up on New Drug Applications.

The plant inspection itself is designed to assure compliance with FDA's current "Good Manufacturing Practices" regulations.

Inspections now cover the following general areas: (*3*)

1. Observation of representative dosage forms through various stages of processing.

2. Education, training, and capability of personnel and condition of facilities.

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[1] See page 36.

3. Control of raw materials, labels, and supplies.

4. Comparison of master formula records with batch records and observation of laboratory testing for adherence to product specifications.

5. Control of manufacturing procedures (e.g., identification and segregation of ingredients; protection against cross-contamination).

6. Procedures to insure sterility.

7. Quality checks on finished products.

8. Inventory control and distribution methods.

During the inspection and upon its completion, opportunities are presented for full discussion of any weaknesses or inadequacies observed. A comprehensive written report is filed, including an evaluation of the manufacturer's overall quality control and production system.

On July 1, 1968, FDA started its new Intensified Drug Inspection Program (IDIP). An IDIP inspection requires the FDA inspector to make an in-depth review of the manufacturing and quality control practices applied to each product produced by the manufacturer. This in-depth review identifies the practices and procedures which may lead to the marketing of drugs of uncertain quality. In effect, the inspector conducts operations analyses to insure that a manufacturer adheres to the Good Manufacturing Practices required by FDA. His efforts are supported by extensive sample analyses of products. The inspector has been trained not only in the enforcement aspects of FDA's mission but reoriented toward a philosophy of openly discussing problems and observations with plant management.

Intensified coverage contemplates that an inspector will spend sufficient time in a selected plant to become thoroughly familiar with all of its operations. It is obvious that the length of time required for this type of attention to a given plant may vary widely, and depends on the number of products manufactured, the size and complexity of the operations, and many other factors. It is estimated that, on the average, 1 man-year would be required per plant for coverage of manufacturing practices exclusive of labeling and promotional operations. (This provides for repeat visits to the plant, as necessary.)

By late in 1968, 91 manufacturers and two commerical quality control laboratories were undergoing IDIP coverage. Seven IDIP inspections were completed, with an injunction obtained against one of the firms and voluntary corrective action taken by the other six.

In general, the step-by-step procedure is as follows:

1. The FDA District Director meets with top management of a firm selected for IDIP, explains the program, and solicits management cooperation.

2. An inspector—or team, in case of a large manufacturer—conducts the inspection operation, remaining in the factory for sufficient time to determine that the firm is operating in full compliance with the law, or—if it is not—what corrective actions are indicated. This may take from several days to several weeks.

3. The inspector outlines in detail to management what is required to produce a satisfactory product.

4. The inspector leaves and returns to the plant after sufficient time for corrective action. Steps 2, 3, and 4 are repeated until FDA is satisfied that the manufacturer is operating in a completely satisfactory manner, or it is concluded that the manufacturer is incapable of operating satisfactorily, in which case necessary court action may be taken.

5. During the above procedures, there may be additional conferences between the FDA District Director and top management of a firm. Also, there may be—and frequently are—recalls and seizure actions to remove from the market any unfit drugs detected during inspection.

The IDIP differs from the traditional FDA inspection operation in that the latter was a spot check conducted for only a few days at widely-separated intervals. The latter did not provide an adequate opportunity to determine in detail the various problem points in the factory. The IDIP also differs from the former spot-checking operation in that it appears to be received more favorably by manufacturers, who recognize that FDA will take legal action if necessary, but has the primary objective of helping them correct undesirable practices without court actions.

While the FDA depends almost entirely upon the USP and NF standards for drugs, the Department of Defense finds it necessary to supplement these standards with additional requirements in its purchase specifications. The DOD also maintains a rigid system of inspection by having resident inspectors present during much of the time that goods are being produced under military contract and further through regular, although unannounced, visits to the plants of suppliers of military goods. This system assures stricter adherence to good manufacturing practices.

The more rigid standards and quality control required by DOD is attributed in part to the special needs of the military, particularly for products which can withstand long storage and exposure to extremes in climatic conditions. On the other hand, DOD inspectors have rejected drugs on less military grounds—such as on the basis of unacceptable variations in potency, unacceptable rates of dissolution, and unacceptable manufacturing practices.

Since DOD acts as a purchaser rather than as a regulatory agency, it is not required to take court action or other legal steps when it finds evidence of substandard products or unacceptable producing methods, nor is it authorized to make public its findings. When such unacceptable conditions are found by DOD inspectors, the department merely rejects the product.

Some products thus rejected by the military may legally enter interstate commerce and be sold to the general public.

Representatives of DOD may communicate their findings to FDA, but this communication between the two agencies is less than optimal.

Product Surveillance.—A second major element in FDA's quality control program is the laboratory testing of representative drug products collected in the marketplace.

At present, most of the testing is done in FDA's 18 regional laboratories. Until recently, all samples were tested individually by laborious manual processes, and considerable laboratory time was expended just in rearranging equipment for each kind of examination.

Despite these handicaps, FDA accomplished 43,388 drug assays in fiscal year 1967. On the basis of these assays, 651 product recalls were initiated (see Table 1). The FDA is convinced that, despite constantly improving process controls, drug quality is still less uniform than it could be.

FDA officials feel that an optimally effective surveillance program should provide for the testing of between 150,000 and 300,000 samples of drugs annually. Achievement of this goal would require increased use of automated test equipment and mass production techniques.

Development of such a testing program is now underway. In February 1967, a pilot operation emphasizing the new techniques was begun in FDA's St. Louis facility. Based upon this facility's early success, FDA is developing a full-scale National Center for Drug Analysis. The Center's activities will not completely supplant the regional laboratories. The latter will still maintain facilities for emergency testing and for routine examinations which cannot be done on an automated or mass production basis.

Table 1

Food and Drug Administration Regulatory Program Data (Drugs), Fiscal Year 1967

Domestic Inspections	16, 169
Domestic Sample Examinations	43, 388
Import Samples Collected	5, 572
Import Detentions	4, 134
Certification Tests (antibiotics and insulin)	21, 391
Recalls	651
Seizures[1]	389
Prosecutions[2]	18
Injunctions	14
Informal Hearings[3]	429

[1] Does not include 45 seizures involving illegal drug sales.

[2] Does not include 312 prosecutions involving illegal drug sales.

[3] These afford the firm opportunity to explain informally why formal court action is not required because of a violation of the law. In most cases, these hearings lead to voluntary corrective action by the firm. Most hearings do not result in court action.

Premarketing Clearance of New Drugs.—Before 1938, the Federal Government had no authority to control new drugs before they were placed on the market. Any Federal action could be taken only after the fact—and possibly only after individuals had been harmed or killed.

In 1938, the first step to rectify this situation came with enactment of the law requiring that clinical data in support of a drug's *safety* be submitted to FDA before the drug could be marketed.

Since 1962, as the second step, the law requires that proof of *efficacy* must also be supplied to FDA before marketing. The law applies not only to new drugs introduced after 1962, but also to those marketed between 1938 and 1962.

A "new drug" has been defined in the Food, Drug, and Cosmetic Act as any drug which qualified experts would not recognize as "safe and effective for use under the conditions prescribed, recommended, or suggested" in its labeling, or one which has been recognized as safe and effective for use under the conditions prescribed but which has not been used under those conditions to a material extent or for a material time.

The law has been interpreted to include new combinations, new therapeutic indications, and new dosage forms of previously established drugs.

FDA's responsibilities in this area are assumed by its Office of New Drugs. Six divisions within this office each process applications in a specific medical specialty area. The office is supported by other FDA units and by outside medical consultants and advisory committees.

The first step to be taken by an applicant is the submission of an Investigational New Drug (IND) application. This must be approved before clinical studies may be undertaken. The IND must include detailed information about the drug's physical and chemical properties; the process by which it is to be manufactured; results of all preclinical (including animal) studies; a proposed plan for human clinical trials; information regarding the training and experience of the investigators; and other related data.

Once the IND has been submitted, clinical trials may be started. The progress of clinical investigation is monitored by FDA through clearly defined phases, from initial testing in human subjects until well after the drug is approved for marketing. In all but exceptional circumstances, the informed consent of subjects participating in the trials must be obtained.

When the IND study has been completed, the manufacturer may submit a New Drug Application (NDA), upon which FDA is required to act within 180 days. The NDA involves additional data relating to manufacturing, marketing, and promotional plans. Methodology for process controls must be outlined, and the manufacturer must assure that each batch of the drug will be equivalent to that upon which the NDA is based. In most cases, the manufacturing facility must be inspected. The proposed labeling (including the required package insert) must be approved by FDA. After NDA clearance, the manufacturer must submit periodic reports upon ongoing clinical studies and prompt reports of any unexpected adverse reactions.

The various phases of IND and NDA may require several years. Five years to complete all the requirements is not considered unusual.

The NDA document is now regarded as privileged information. It is not made public by FDA, even after expiration of the drug patent. A manufacturer holding an effective NDA may, however, unilaterally release this information to another manufacturer. The latter, after demonstrating his capability of producing the drug, may base his application to market the same product upon the original clinical data.

Any manufacturer may submit an NDA at any time. In theory, he is required to provide exactly the same kind of data in support of the drug's safety and efficacy as was the original NDA holder. In practice, however, the literature generally includes reports of a number of pharmacological and clinical studies by the time a drug has been in long use. These may be cited and are generally accepted in support of the application. In some cases new clinical evidence of safety and efficacy is required. In these secondary NDA's, FDA is concerned primarily with the way in which the formulation is designed, the applicable process controls, the capability of the manufacturer, and plans for labeling and distribution.

As noted above, the basic NDA document is considered to be the property of the applicant. Whether or not the scientific and manufacturing data it contains should be made public upon expiration of the drug patent has recently been discussed. (*11*)

Certification of Insulin and Antibiotics.—In the case of insulin and antibiotics, special provisions have been established for certification of each batch of the product.

FDA certification was first authorized for insulin in 1941, shortly after the patent expired. Congress felt that, in the case of this life-saving drug, certification in advance of distribution was in the national interest.

The same reasoning was applied to penicillin in 1945 and, by subsequent amendments, to all antibiotics.

Present legislation authorizes the Secretary of Health, Education, and Welfare to waive antibiotic certification if a manufacturer has established a performance record which includes 50 consecutive batches of compliant products in a given class within 18 calendar months. No exemptions have been granted under this authority.

The certification program appeared to have been adequate until late in 1967. During that summer Parke, Davis & Co. conducted comparative physiological trials of its chloramphenicol product (marketed under the brand name of Chloromycetin) with chemical equivalents marketed under the generic name by several other manufacturers. Using blood levels, urinary excretion rates, and dissolution rate data, the company found that the absorption of its product was not matched by the performance of the competitive generic products.

FDA reviewed the Parke, Davis data and verified the results with its own studies. On the basis of these findings, it suspended certification of all chloramphenicol products except that made by Parke, Davis. It has since specified the Parke, Davis chloramphenicol as a "reference product" and has required that evidence in support of certification of any other generic product must show that the generic product produces a blood concentration curve not significantly different from the reference product. A detailed clinical protocol has been developed for that purpose.

This action represented FDA's first effort to require direct evidence of biological equivalency. It has implications not only for other certifiable drugs in which equivalency might be questioned, but also for noncertifiable drugs upon which New Drug Applications are in effect. Using its chloramphenicol action as precedent, FDA could require that each prospective supplier of an NDA drug demonstrate that his product produces blood levels (or other evidence of physiological availability) similar to that upon which the original NDA was based. If the physiological availability were significantly dissimilar, then direct clinical evidence could be required to demonstrate the efficacy of the product.

Self-Certification.—In 1967, FDA began a regulatory experiment—in this case involving a food processing firm—in which quality control personnel developed standards for good manufacturing practices and product quality that were acceptable to FDA in lieu of routine plant and product inspection. After further experience, FDA hopes to extend the program to other food processors.

FDA officials have also expressed their intention to develop a similiar pilot program in the prescription drug industry.

The NAS/NRC Drug Efficacy Study.—As noted above, the 1962 Amendments to the Food, Drug, and Cosmetic Act required proof of efficacy for all "new drugs" marketed after 1938. This requirement was swiftly reflected in FDA's NDA procedures for all products first marketed after 1962. But the amendments also required reappraisal of the effectiveness of drugs approved for safety alone during the 24-year period 1938–62. FDA was thus faced with the enormous task of retrospective review at a time when it had to cope with increased requirements for the current output of new drugs. In this situation, the agency turned to the National Academy of Sciences-National Research Council, and in July 1966 a contract was signed for the necessary investigation.

As soon as this agreement was reached, FDA invited the industry to submit briefs on the efficacy of all 1938–62 drugs that they wished to retain on the market. Ultimately 237 firms responded with presentations on some 3,600 drug formulations. The majority of these carried therapeutic claims for a variety of medical conditions. It is estimated that between 10,000 and 15,000 therapeutic judgments were required.

The work of evaluation of these claims was assigned by NAS/NRC to 180 experts assembled in 30 panels covering the main categories of drug actions. The panels were supported by a professional staff of 14 members, including 10 Public Health Service physicians.

The 1962 amendments called for "substantial evidence," meaning "evidence consisting of adequate and well-controlled investigations, including clinical investigation, by experts qualified by scientific training and experience to evaluate the effectiveness of the drugs involved . . ."

The panels sought the requisite evidence in the material submitted by sponsors of the drugs reviewed, in additional documentation solicited from the sponsors, in the files of FDA, and in pertinent medical literature. In many cases, authoritative data were scanty. In these instances, the panels had to supplement their review with deductive reasoning and the individual clinical experiences of their members and consultants.

The terms of the contract called for a categorical rating of "Effective," "Probably Effective," "Possibly Effective," or "Ineffective" for each therapeutic indication claimed for the use of each drug. Later a category of "Effective, But——" was added. In addition to citations of appropriate literature, the panels appended to many of their reports more general comments on the attributes of selected classes of drugs, on therapeutic guidelines in certain categories, and on other specific problems uncovered in the course of their reviews.

Although the panels were not assigned responsibility for making determinations of comparative efficacy, in many cases their reports included statements of opinions on comparative therapeutic effectiveness. Similarly, they were not required to evaluate the safety of these drugs *per se*, yet many reports specifically commented upon safety in respect to each indication for its use.

Formulation factors which have been outlined in earlier sections of this chapter were expected to influence the validity of the panel reviews. The effectiveness of a particular formulation can be evaluated only on clinical data derived from administration of that specific product, and unfortunately the identity of the particular product used in a clinical trial was often inadequately documented. As a consequence, among drugs in which clinical equivalency has been questioned, there may be reason to question the evaluations of efficacy.

By mid-1968, the panels had nearly completed their work and the majority of reports were expected to be filed with FDA by the end of the year. These reports will be transmitted in confidence to FDA, but it has been agreed that, since they constitute a valuable audit of the state of the art in drug therapy, they should be made freely available to industry and to the medical community as soon as appropriate action has been taken upon them.

Division of Biologics Standards (DBS)

DBS complements the regulatory functions of FDA in the area of biological products made from infectious or potentially infectious agents (vaccines, antitoxins), therapeutic sera, blood and blood derivatives, allergenic products, and analogous products, and arsphenamine and its derivatives.

Its regulatory activities derive from Public Law 58–244, signed by President Theodore Roosevelt in 1902, which assigned to the Secretary of the Treasury (ultimately, through a series of amendments, to the Secretary of Health, Education, and Welfare) responsibility for controlling the manufacture and sale, barter or exchange, interstate, for import and export, of licensable biologics.

These functions were originally delegated to the Hygienic Laboratory of what was then the Public Health and Marine Hospital Service. Since 1937, they have been part of the National Institutes of Health. In 1955 the biologics group was given separate Division status in the National Institutes of Health.

The number of drugs controlled by DBS is considerably smaller than that of FDA. The Division regulates 220 suppliers, in contrast to the 2,000 firms registered with FDA. Of these 220, about 150 are blood banks engaged in interstate commerce and, except for processing blood for transfusion to humans, are not engaged in drug processing. The actual number of DBS-controlled manufacturers thus is closer to 70.

In many ways, DBS drug control resembles that of FDA. Like FDA, the Division has procedures for new drug clearance, regulating good manufacturing practices, plant inspection, and drug sampling. It differs, however, in some important respects:

1. *Licensure.*—FDA approves New Drug Applications rather than issuing licenses to manufacturers. FDA requires registration before a manufacturer can enter his drugs into interstate commerce. FDA does not require plant or product inspection before approving drugs. In contrast, DBS requires premarketing inspection and qualification for license not only of the plant but of each product proposed for distribution.

2. *Duration of approval or license.*—FDA drug approvals and DBS licenses are not subject to time limitations. FDA approvals remain in effect until challenged for lack of safety or effectiveness in use; DBS licenses remain in effect until challenged for failure to meet agency prescribed standards of safety, purity, and potency.

3. *Frequency of inspection.*—FDA regulations provide for plant inspection at 2-year intervals. DBS regulations provide for annual inspection.

4. *Nomenclature.*—FDA relies mainly upon an independent agency, the United States Adopted Names Council, to provide official names for new products. DBS designates an official name for each newly licensed product. DBS names, however, are not difficult to determine since they are essentially generic in that the name always features the principal biologic agent involved (e.g., adenovirus vaccine).

5. *Labeling and advertising.*—DBS does not monitor the advertising of biologics. It does control package labeling, however, and requires that the official name of a preparation appear on the container and package label in type face at least as large and as distinctive as any accompanying trademark or trade name. It also requires that the official name be placed above any trademark or trade name. The FDA

labeling and advertising authority applies equally to labeling and advertising of licensed biologicals.

6. *Penalties.*—Both FDA and PHS statutes provide for criminal penalties for violations (for FDA, 1 year and $1,000; second offense, 3 years and $10,000—for PHS, 1 year and $500). The PHS statute does not provide for such violations as does the FDA for adulteration or misbranding, nor for seizure or injunction, but these provisions of the FDA statute apply equally to licensed biologicals.

Chapter 8

TASK FORCE EQUIVALENCY TRIALS

In the fall of 1967, the Task Force initiated a program to determine scientifically the biological equivalency of a number of chemical equivalents. A major phase of the investigation was an attempt to determine whether any observed differences in biological equivalency could be related to differences in the physical or chemical characteristics of the products.

At the outset, it was recognized that such trials were urgently needed for relatively few drugs. For example, as noted elsewhere, (*25*) among the 409 products most widely used by the elderly—and which accounted for about 88 percent of all out-of-hospital prescription drugs dispensed to this group, there were only 89 which were dispensed under brand name but could have been dispensed under generic name from one or more additional suppliers. An additional 30 were actually dispensed under generic name.

Among these, the priority for clinical study was determined on the basis of one or more of the following criteria:

1. The product is generally considered as a "critical" drug—that is, required for the control of a disease or the relief of severe, disabling symptoms.
2. It is generally dispensed in solid form—as a tablet or capsule—rather than in solution.
3. The active ingredient is relatively insoluble.
4. Particular attention should be given to those drugs which had previously been the subject of reported or suspected nonequivalency or therapeutic failure.

A number of drugs meeting these criteria—together with a few others selected for special study—were selected by the Task Force in consultation with representatives of clinical medicine, pharmacology, pharmacy, brand name and generic name manufacturers, the Food and Drug Administration, and other governmental agencies. Among these drugs, listed in alphabetical order, were the following:

Aminophylline
Bishydroxycoumarin
Chloramphenicol
Chlortetracycline
Diethylstilbestrol
Diphenhydramine HCl
Diphenylhydantoin
Erythromycin
Ferrous sulfate
Griseofulvin
Hydrocortisone
Isoniazid
Meperidine HCl
Meprobamate
Oxytetracyline
Para-amino-salicylate, sodium
Potassium penicillin G
Potassium penicillin V
Prednisone
Quinidine
Reserpine
Secobarbital sodium
Sulfisoxazole
Tetracycline
Thyroid
Tripelennamine HCl
Warfarin sodium

(It must be emphasized that inclusion in this list does not necessarily indicate that any or all generic-name products are or are not biologically equivalent.)

Biological equivalency studies on the first of these products in human volunteers began late in 1967 in the FDA laboratories, at Georgetown University under an FDA contract, and at the Public Health Service Hospital in San Francisco. In each instance in which adequate analytical procedures were available, blood levels were determined at appropriate periods after the product had been given by mouth.

By October 1, 1968, the situation was as follows:

- It had been ascertained that lack of biological equivalency existed to a degree which was judged to be of probable clinical significance in the case of one drug for human use—chloramphenicol. The nonequivalent products were promptly removed from the market, either by FDA action or by action of the respective manufacture. (*2*, *10*, *17*, *26*)
- No clinically significant lack of equivalency had been noted among isoniazid products. (*16*)
- Different absorption rates were noted in the case of different forms of diphenylhydantoin and sulfisoxazole, but the clinical importance of these differences was still undergoing study. (*17*)
- In addition, on the basis of its own studies, one manufacturer elected to remove its erythromycin tablets from the market. (*27*)
- For many of the other drugs on the priority list, suitable methods had been developed and clinical trials were underway.

In the case of other drugs included in the above list, or others selected for investigation, it is expected that the test results will be published in medical or scientific journals, and that products will be removed from the market as an essential step in improving the quality of health care where legally and clinically significant nonequivalence has been established.

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PART C

FORMULARIES

Chapter 9

INTRODUCTION

With the possible exception of chemical and therapeutic equivalency, few aspects of proposed drug insurance plans have been the subject of more heated controversy than has a restrictive drug formulary.

The use of a formulary has been termed an absolute essential for rational drug therapy, a guide without which physicians cannot hope to keep abreast of new information on old drugs and the profusion of new drugs and their related advertising and promotion, a vital necessity for a financially sound insurance program and for economical hospital operations, an urgently required tabulation of drug specifications and standards, and a valuable guide to current prices. (*2*, *9*, *12*, *15*, *19*)

On the other hand, its use has been decried as a destructive infringement on the traditional right of the physician to prescribe according to the dictates of his professional judgment, a maneuver to require generic prescribing, an attack on brand-name drugs, dictatorship by the Federal Government (or a State government, a hospital administrator, or a union), and a dangerous effort to control drug therapy by means of price rather than quality. (*13*)

One of the obvious characteristics of the formularly dispute—and perhaps one of the main reasons for it—is the lack of any visible agreement among the disputants on what particular kind of formulary they are proposing or opposing. Further, there is no apparent agreement on what a formulary is—or should be.

Strictly defined, a formulary is simply a compilation of formulations—a listing of pharmaceutical substances, formulas, and dosages. Of all the definitions, this has probably the least currency. Instead, a formulary is apparently considered to be any one of the following:

A list of *widely-used* drugs, with standards of purity, indications, and contraindications.

A list of *approved* drugs (as established by a government, a hospital, or an insurance plan).

A list of *recommended* drugs (as established by an individual, a group of experts, a medical society, a government, a hospital, an insurance plan, or a group of advertisers).

At this point, it appears difficult if not impossible to present a precise definition which will be universally accepted. In this section, the word formulary will be used to indicate a drug listing restricted in order to achieve more rational prescribing, or economy, or both.[1]

History

The use of formularies to serve as guides to optimum drug therapy probably stems from the herb lists and almanacs of the early middle ages. (*5*, *14*)

In 1499, the *Nuevo Receptario*—perhaps the first known pharmacopeia—was published in Florence, Italy, and its use made obligatory for members of the Florentine medical guild. Early formularies were published in Austria in 1564 and in Germany in 1546, 1564, and 1565. The first pharmacopeia in England was the *Pharmacopoeia Londinensis* in 1618, which emphasized optimum therapy. In 1778, the *Lititz Pharmacopoeia* was used by the Continental Army in the United States.

These early formularies presented approved formulas for various drug preparations, and served as guides both for the pharmacists who compounded the medicines and the physicians who prescribed them. They did little, however, to set standards of quality for either the ingredients or the finished products.

As new formularies and pharmacopeias appeared, and old ones were revised, the need for quality standards became apparent, and a major function of formularies became the establishment of such standards. This role became increasingly emphasized in the new publications, such as the *United States Pharmacopoeia* (1820),[2] the *British Pharmacopoeia* (1864), the *National Formulary* (1888), and the *Canadian Formulary* (1905).

In the United States, the importance of formularies was heightened by the 1965 Social Security amendments, which permit Federal reimbursement for drugs dispensed in hospitals using a formulary system.

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[1] See also p. 12.

[2] Later spelled as Pharmacopeia.

Chapter 9

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These early formularies presented approved formulas for various drug preparations, and served as guides both for the pharmacists who compounded the medicines and the physicians who prescribed them. They did little, however, to set standards of quality for either the ingredients or the finished products.

As new formularies and pharmacopeias appeared, and old ones were revised, the need for quality standards became apparent, and a major function of formularies became the establishment of such standards. This role became increasingly emphasized in the new publications, such as the *United States Pharmacopoeia* (1820),[2] the *British Pharmacopoeia* (1864), the *National Formulary* (1888), and the *Canadian Formulary* (1905).

In the United States, the importance of formularies was heightened by the 1965 Social Security amendments, which permit Federal reimbursement for drugs dispensed in hospitals using a formulary system.

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[1] See also p. 12.

[2] Later spelled as Pharmacopeia.

Chapter 10

AMERICAN FORMULARIES

The official compendia of standards in this country include the *United States Pharmacopeia* (USP), the *National Formulary* (NF), and the *Homeopathic Pharmacopoeia of the United States* (HPUS). The latter publication is mainly of historical interest although it is still published for the dwindling numbers of homeopathic practitioners.

These formularies, particularly USP and NF, are officially recognized in the Food and Drug Acts of 1906 and 1938 as sources of uniform drug standards concerning strength, quality and purity.

U.S. Pharmacopeia *(10, 11)*

The *U.S. Pharmacopeia* is the oldest of the official American compendia, and has been published regularly since 1820. Its Board of Trustees and Revision Committee members are selected at USP conventions held every 10 years. The convention is composed of delegates representing all schools of medicine and pharmacy in the United States, all State and national medical and pharmaceutical associations, several Federal agencies (including the Food and Drug Administration and the Public Health Service), and professional or trade associations.

Although the first convention was composed of physicians, pharmacists were invited to the second meeting and subsequently administration of the USP has been mainly in the hands of the pharmacy profession. The Revision Committee now consists of 20 physicians and 40 pharmaceutical scientists.

Until 1940, the USP was published at 10-year intervals. Since then, it has appeared every 5 years.

New specifications may be introduced during the 5-year period an dannounced through appropriate supplements.

Between meetings, policy is in the hands of the Board of Trustees. Based on this policy, the Revision Committee determines the contents of the two editions prepared during its 10-year tenure. Medical members are responsible for selection of those drugs to be included in each publication. In the USP edition to be published in late 1969, 1,128 drug forms will be listed. Of these, 855 will be carried over from the last edition.

Selection of drugs is considered to be based entirely on therapeutic usefulness. The selection process is delegated to the medical members of the committee, who determine from among the drugs that are in use, those which are well established and represent what they consider to be the best teaching and practice of medicine.

Once the selection has been completed, the pharmaceutical members of the committee begin the process of establishing standards—a task which involves a considerable amount of independent study and laboratory testing. The USP, in cooperation with the American Medical Association and the American Pharmaceutical Association, supports an independent laboratory—the Drug Standards Laboratory—for work on standards.

The makeup of the USP remains roughly the same. It provides detailed monographs on every listed drug, including dosage forms, applicable tests, a description of tests of more general application, procedures for assay, specifications for various reagents, and other supporting data.

Programs of the Trustees and the Revision Committee are financed solely from the sale of the USP and from fees for distribution of USP Reference Standards. The pharmacopeia is circulated widely in the United States and overseas, with a total circulation now estimated at around 70,000.

No price information is included.

The National Formulary *(3, 4)*

Of more recent origin than the USP, the NF contains monographs on completely different drugs from those included in the USP, and on some drugs which have been dropped from a previous USP listing. Many new drugs are listed initially in the NF and included later in the USP.

Unlike the older compendium, the NF originated entirely within the pharmacy profession, and is published by the American Pharmaceutical

Association. Begun in 1888, it is now in its twelfth edition. It is issued every 5 years at about the same time as the USP, with frequent supplements. There is enough overlap in membership on the revision committees of the two books to ensure optimal coordination of their functions.

Responsibility for the formulation of policy and the preparation of each new edition resides with the NF board, which is selected under the authority of the American Pharmaceutical Association.

For most of its 80 years, the guiding principle for admission of a drug to NF was its "extent of use." In 1961, the NF Board decided that consideration should be given only to "therapeutic value." The drugs for inclusion are selected by a 20-member committee of admissions, which is composed primarily of physicians and pharmacologists.

In the next edition of the NF, 1,041 drug forms will be listed, including 815 carried over from the present edition.

The NF follows the same format as the USP in listing tests, dosage forms, procedures for assay, and other data developed with the assistance of a 50-member committee on specifications, which is composed primarily of chemical, physical, and biological scientists. The Drug Standards Laboratory, supported jointly by the American Pharmaceutical Association, USP, and the American Medical Association, also provides information on testing and standards for the NF.

As in the case of the USP, the NF program is financed through sale of the compendium and fees from NF Reference Standards. Circulation of each edition of the NF is approximately 60,000.

No price information is included.

Homeopathic Pharmacopoeia of the United States

This formulary, made official by the Federal Food, Drug, and Cosmetic Act of 1938, has only limited circulation. It was first published in 1897.

Homeopathy, introduced by Samuel Hahnemann in Germany at the end of the 18th century, is the practice of treating a disease by drugs which are capable of producing in healthy persons symptoms like those of that disease. The drugs are administered in minute doses.

Published by the American Institute of Homeopathy in Philadelphia, the seventh edition of the formulary was published in 1963–64. It contains approximately 685 drug products. The medicines, with heavy emphasis on plants as a base, are listed by Latin name. The format includes history, preparations, characteristics, and tinctures or dilutions of the preparations. The 1,500 homeopathic practitioners usually formulate the drugs themselves, although there are still a few homeopathic pharmacies in operation.

AMA Publications (*7*)

During the late 1950's, the American Medical Association became concerned with the problem of supplying current drug data and evaluations for members of the medical profession. Since publication of an AMA drug book began, the name has been changed several times.

New and Non-official Remedies (NNR), first published in 1907, became *New and Non-official Drugs* (NND) in 1958. Drugs were listed by pharmacological groups. In 1965 the AMA Council on Drugs first produced *New Drugs* as an annual publication, with drugs listed by therapeutic classification. The Council is now planning to publish *AMA Drug Evaluations*, which is scheduled to appear for the first time early in 1969. (*1*)

AMA Drug Evaluations is expected to include all the drugs listed in the USP and *New Drugs*, plus those other drugs which are most commonly administered or prescribed by physicians. Inclusion in this volume, as in previous AMA publications, will not necessarily signify AMA approval. Drugs will be listed by therapeutic category, and identified by both generic and brand name.

Monographs will include indications, contraindications, dosages, administration, adverse effects, course of therapy, and general clinical information.

No price information is included in these publications.

Accepted Dental Remedies

Published every 3 years by the American Dental Association, this formulary attempts to provide dentists with current information on drugs used in dental treatment. The ADA Council of Dental Therapeutics selects and evaluates the drugs on its own initiative or on request.

Chapter 11

STATE FORMULARIES

After some 5 to 30 years of experience with drug vendor activities under various general welfare programs, and more recently under the Medicaid program, State welfare agencies are still divided on the use of formularies to improve the quality of health care, standardize drug selection, and control costs.

Under earlier welfare programs, drug reimbursement was usually carried out at the county level, with case-by-case review of prescriptions. Since the initiation of federally supported programs, however, the number of eligible beneficiaries and the scope of services have been vastly expanded. The monitoring of prescriptions by case review, as traditionally conducted, no longer appears to be feasible.

Few States have allocated sufficient funds for a comprehensive drug service. Accordingly, many of those with major programs have found they must limit drug usage, either by listing reimburseable drugs in a formulary, or by listing drugs which are not reimbursable, or by other means.

Of the States with vendor drug programs, thirteen—California, Georgia, Hawaii, Illinois, Kentucky, Louisiana, Missouri, New Mexico, Oregon, Pennsylvania, Tennessee, Washington, and West Virginia—have formularies. (*17*, p. 36)

Formulary Structure

A "closed" formulary, listing all reimbursable drugs, is used in California, Hawaii, Kentucky, Missouri, New Mexico, Oregon, Tennessee, and Washington. All of these "closed" formularies have an "escape clause" which permits prescribing of non-listed drugs by special authorization for unusual situations.

Illinois and Georgia use a more open formulary which permits reimbursement for an unlisted drug providing there is no equivalent in the formulary.

Pennsylvania will reimburse for any drug but uses its formulary as a noncompulsory guideline for physicians.

As a formulary, New Mexico uses the *Physicians' Desk Reference*, a widely circulated commercial reference, in which the drugs are listed through advertisements by drug manufacturers.[1]

Louisiana and West Virginia use lists of disease categories rather than formularies. Any drug used in the treatment of these specified serious and chronic illnesses is reimbursable.

Number of Drugs.—The number of single entities in these State formularies varies from approximately 100 in Kentucky to almost 2400 in Pennsylvania. The various drug formulations of the individual drugs make the number of entries even larger; for example, the single drug phenobarbital may be listed as three products—phenobarbital tablets, 15 mg.; phenobarbital tablets, 30 mg.; and phenobarbital elixir.

Advisory Committees.—As required by the Medicaid legislation, all States with drug vendor programs—with or without formularies—have drug advisory committees which provide policy recommendations. Generally there is both a Medical Advisory Committee and a Pharmacy Advisory Committee.

Four States have specific committees that recommend drugs for the formulary or drug list. In California, the addition of drugs to the formulary must be recommended by the Drug Advisory Committee and approved by the Office of Health Care Services. Many of the States also have medical services committees, pharmacy services committees, and consultant physicians and pharmacists to advise on services and policy. The committee members—physicians, dentists, osteopaths and pharmacists—are usually recommended by their respective professional organizations.

While the advisory committee may recommend policy and procedures, the final decision is usually made by the Director of the Welfare Department, who may make the budget a decisive factor. There are, however, a few States which have delegated this authority to the Health Department.

Formulary Revisions.—Requests for formulary revisions are generally submitted by practicing physicians and others to the Welfare Department or to the appropriate advisory committee. A manufacturer may also request that a drug be admitted to the formulary. (*17*, p. 49)

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[1] See page 50.

During one of the early years of its Medicaid program, Kentucky compiled a list of nonformulary drugs that had been requested by two or more physicians. The list was sent to each physician in the program with the request that he list, in priority, ten drugs he would like to see added to the existing formulary. The replies were referred to the formulary advisory committee. As a result, 40 drugs were added to the list.

Formulary Exclusions.—In their formularies, most States list classes or types of drugs that are not reimbursable. These may include one or a combination of the following categories: over-the-counter items, household staple drugs, nonnarcotic analgesics, multivitamins, antiobesity drugs, sustained release medications, tranquilizers, and antacids.

Exclusion may also be specified in some States for drugs that are furnished at no charge under other programs or agencies, such as drugs used in the treatment of venereal disease, tuberculosis and mental disease, as well as vaccines and immunizing agents which are furnished by State, county, or local health departments.

Limitations on Prescribing.—Many States limit the prescribing and dispensing of drugs listed in their formularies through restrictions on quantity, number of refills, and maximum price for each prescription.

The maximum reimbursable quantity for each drug may be included in the formulary.

The number of refills permitted under the program is usually specified. Only five States do not recognize refills at all, presumably requiring the patient to return to the physician for a new prescription each time.

A dollar limitation may be placed on prescriptions in some programs. This may average from $9 to $10 a prescription, or from $10 to $20 a month, per beneficiary.

States may utilize only one or a combination of these restrictions. For example: Louisiana restricts refills only; Pennsylvania, however, not only permits no refills, but sets a dollar limit on the prescription.

Nomenclature.—The Medicaid formularies may list drugs by generic name, brand name, or both. If the information on prescribing price or quantity limitations is included, it is usually entered under the generic name.

Generic Prescribing.—Some States encourage generic prescribing by basing reimbursement costs on the price of generic-name drugs. Many States place no limitation on the choice of drugs other than requiring that they meet USP and NF standards if applicable. West Virginia requires that "payment from the Medical Services Fund is limited to drugs marketed by pharmaceutical companies involved in basic medical research, product development, and marketing."

Pricing.—Some States list the drug prices permitted under the program by units, such as per tablet, capsule, vial or ounce. Other formularies include a table for a percentage markup based on the total acquisition cost. For example, the State may permit a 66⅔-percent markup on items with an acquisition cost of from $1 to $5 and a 50-percent markup on items from $6 to $9. A few States allow the acquisition cost plus a set dispensing fee. Missouri sets the fee on the basis of the prevailing price in the community.

Advantages and Disadvantages

A survey of 10 selected States (*17*, p. 87) showed the following:

Six of the 10 States were using a formulary—California, Georgia, Illinois, Missouri, Orgeon, and Pennsylvania. They credited its use with cost control, along with accounting efficiency, frequently through the utilization of computers.

In at least some of these States, the situation regarding the size of the formulary appeared to be fluid: several were considering an expansion in the number of reimbursable items, while others were considering a reduction.

Precise figures to demonstrate cost savings were unavailable.

Where the use of a formulary appeared to be generally acceptable to physicians, it was obvious that the selection of items in the formulary had been determined by physicians, or at least with their formal or informal approval. The formulary thus represented a verdict of their peers, rather than a dictate of governmental officials.

The other four States—Minnesota, Ohio, Rhode Island, and Utah—had elected not to use a formulary, although Utah and Minnesota had previously utilized one. All four cited administrative costs, impracticality, and physician opposition as the principal reasons.

Chapter 12

OTHER FORMULARIES

Private Insurance Programs

Some nongovernmental drug programs—such as Prepaid Prescription Plans, Inc., and Paid Prescriptions, Inc., of California—involve no formulary restrictions, and provide reimbursement for essentially any prescription drug. (*17*, pp. 119, 122).

There are others which are based on a formulary. For example, the Kaiser Foundation Health Plan (*17*, p. 131) utilizes regional formularies which serve primarily to standardize therapy. Physicians are not limited to the formulary, but only the brands stocked will be dispensed. Cost control is effected through bulk purchase, by bid, of the least expensive chemical equivalents wherever available, and the computerized inventory control permitted by limiting the number of items.

Group Health Association, in Washington, D.C. (*16*), uses a drug list which places no restriction on drug choice, but does use generic identification.

Group Health Cooperative of Puget Sound (*17*, p. 129) uses a formulary to enhance rational drug therapy and control prices. It involves a comprehensive generic formulary of about 2,000 items, listed alphabetically by therapeutic functions and indexed by both generic and brand names. New drugs are reviewed every six months by a pharmacy committee, with changes reported in a supplement.

The United Mine Workers (*17*, p. 127) uses several formularies for different areas. The drugs included are based on the needs of the recipients of the area. Some areas list specific drugs, while others list chronic diseases for which they will authorize payment for drugs.

Hospital Formularies

The Pharmacopeia of New York Hospital, considered the first private civilian hospital formulary in the United States, was first published in 1816. Since then, many American hospitals have developed formularies for their own use, partly as a guide to their staff physicians, and partly to cope with the inventory problems of their own pharmacies. (*5*)

The importance of such formularies was heightened by the Social Security Amendments of 1965, which stipulated that reimbursement for drugs used in the treatment of hospitalized patients in the Medicare program would be approved only if such drugs were included in USP, NF, or similar standard compendia, or if they were in a formulary adopted in an accredited hospital by action of its Pharmacy and Therapeutics Committee.

Enactment of the Federal Medicare legislation was followed in December 1965 by a resolution of the Joint Commission on Accreditation of Hospitals and the American Society of Hospital Pharmacists to add "pharmacy and therapeutics practices to the functions of an accredited hospital." (*8*)

Since then, the American Hospital Association, the American Society of Hospital Pharmacists, the American Medical Association, and the American Pharmaceutical Association have joined in stating: "A hospital formulary system is considered important in drug therapy in hospitals. In the interest of better patient care, its adoption by hospital medical staffs is recommended." (*15*)

Most current hospital formularies are drug lists developed by the hospital's Pharmacy and Therapeutics Committee. (*5*, *16*) They are used principally to refer the prescribing physician to drugs which are reimbursable and which consequently are stocked in the pharmacy. They represent the considered selection by a committee of staff physicians and pharmacists. Although the drug list may be more or less restricted, provisions are usually made for exceptions to be authorized for unusual conditions. Most hospitals recognize that there may be justifiable reasons for a physician to prescribe a nonformulary drug for a particular patient.

Many hospital formularies encourage or require prescribing and dispensing of low-cost chemical equivalents wherever these are available.

Generally, hospital formularies have been found acceptable by most staff physicians if the Pharmacy and Therapeutics Committee of the hospital is active. This may be related to the fact that the selection of drugs is made by the physicians themselves, or their representatives, and thus represents judgment by peers rather than any decision by hospital administrators or any nonmedical group.

The American Hospital Formulary Service of the American Society of Hospital Pharmacists, first published in 1959, is provided to assist Pharmacy and Therapeutics Committees in preparing their own formularies. It consists of drug monographs developed and reviewed by leading medical scientists, clinicians, hospital pharmacists, pharmacologists, and other professionally qualified persons affiliated with hospitals. The monograph of each drug is listed under its generic name, with common synonyms and brand names indicated. Pertinent information is given on physical and chemical characteristics, actions, uses, and dosages. The monographs are arranged pharmacologically. Supplements are issued periodically to keep the material up to date.

Foreign Formularies

Many nations have long utilized formularies or similar lists to provide standards of quality, indications and contraindications, and similar information. Among these are such publications as the *British Pharmacopoeia*, the French *Codex*, and the *Deutsche Arzneibuch*.

In addition, many countries have set up special formularies to develop more rational prescribing and economies in their national drug programs.

In Australia (*17*, p. 137) and New Zealand (*17*, p. 184), for example, formularies are used primarily as a method of cost control. The drug lists are restrictive, with medicines listed alphabetically by generic name. The Australian government has no authority to set prices but uses inclusion in the formulary as a means of price control. If the price is too high, the drug may be dropped from the list. New Zealand negotiates prices but will pay only for the price of the chemical equivalent.

The lists of Norway (*17*, p. 187), Sweden (*17*, p. 190) and Denmark (*17*, p. 169) are structured to provide essential drugs for serious diseases. All three countries maintain strict control on the distribution of drugs. The formulary lists diseases and drugs, and a drug is reimbursable only when used in the treatment of one of these chronic and serious illnesses.

The Netherlands (*17*, p. 180) uses formularies to enhance rational prescribing, as well as to control costs. One formulary, distributed to hospitals, lists those drugs that may be dispensed in such institutions. A second goes to the pharmacist, who fills the prescription written by a physician. The third goes to doctors who dispense medicines in their offices.

In France, Great Britain and West Germany, the formularies have been open-ended. In Great Britain and West Germany, the formularies are noncompulsory, with West Germany reimbursing for 80,000 different drugs, medicines, and preparations. The French have the most exhaustive of national formularies. All but 3 percent of the drugs sold in the country are listed in the *Codex*, the name for the national formulary. France, however, has already made cutbacks in the overall health program as a result of large deficits and has appointed a committee that will be concerned with compiling a more restrictive drug formulary (*17*, p. 172).

Currently, Great Britain is considering a compulsory national formulary with a more restricted list of drugs to help control soaring costs in its health program (*17*, p. 175).

West Germany is considering the introduction of a compulsory formulary for the national health insurance program (*17*, p. 193).

Drug Lists

Other publications—drug lists rather than formularies—serve as price catalogs, or as advertising media. Several have a wide circulation among pharmacists and physicians.

Red Book.—This annual publication, prepared by *Drug Topics*, provides wholesale prices of nearly all drug products and over-the-counter items. It is distributed to more than 70,000 pharmacists and hospitals at a cost of $10 per copy. In order to keep the issue current, the publisher sends questionnaires to about 4,000 manufacturers four times a year.

Products are listed alphabetically by the name under which they are usually marketed. Advertisements are set into the product listing, and may range from one item to a company's whole pharmaceutical line.

Blue Book.—Similar to the Red Book, the *American Druggist Blue Book* is an annual reference catalog that provides wholesale prices for drugs, together with descriptive data on many items.

The largest section of the book is devoted to drug products. Other sections include professional pharmacy information, poison control centers, dosage charts, and an index of manufacturers. In the product section, drugs are listed by the name under which they are marketed.

The book sells for $9 a copy.

Physicians' Desk Reference (PDR). This widely circulated—and widely used—reference book is published annually and provided free of charge to all physicians and hospitals. (Copies can be purchased, however, for $10 each.) Circulation is estimated at 450,000.

The listings in the book are paid advertisements from drug manufacturers.

The information is taken, often verbatim, from the package inserts that must be included in the drug package under FDA law.

Approximately 2,500 drugs were listed in the last edition. Low-cost generic products have been rarely, if ever, listed.

No price information is included in PDR.

Advertising rates are based on a schedule of $875 to $2,500 per page.

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